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SOME CLINICAL CHANGES IN BEHAVIOR ACCOMPANYING ENDOCRINE DISORDERS[1]

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Hormones are of complex chemical structure and appear rather late in the evolutionary development of animals. They are secreted by certain ductless glands and are carried to "target organs" by the blood stream to stimulate or depress function. By thus influencing metabolic processes in a selective way, they have an important effect on the behavior of the organism. In general they exert a strong influence on the amount of behavior activity; in particular they influence certain patterns of behavior, such as those seen in fear, love, maternity and mating. Hoskins (12) has given an excellent summary of the pertinent facts up to 1945 in his *Biology of Schizophrenia*, where he points out that disturbances of hormonal physiology have often been postulated as important etiological factors in schizophrenia.

I would like to digress a moment to praise this book of Hoskins'. Its 191 pages contain a brilliant summary of the present knowledge about schizophrenia; and with this he gives a brief exposition of his own work from 1926 to 1945 on the neuro-endocrine aspects of this disease. As a biologist and physiologist he illuminated a difficult problem for psychiatrists. It was his spade work that made possible the important advances of the last few years on the relationship of hormones to psychiatry. Three papers recently published in Psychosomatic Medicine will bring the reader up to date on this controversial subject (2, 3, 20).

SPONTANEOUS CLINICAL PICTURES

Hyperthyroidism (Graves' Disease) is probably the syndrome best known to physicians that illustrates change in behavior apparently due to hyperfunction. These patients become irritable and restless; they are emotional and easily startled, but in spite of fatigue the mood is often euphoric. In rare instances this excitable state may go over into a "thyroid storm" (15). Occasionally profound mental changes supervene in which the patient shows, one after another, practically all the symptoms of schizophrenia and manic-depressive psychosis.

The marked mental retardation seen in cretinism and sometimes in juvenile myxedema cannot be explained on the basis of thyroid deficiency alone; it is better to consider it the result of a general interference with the development of the brain and body. The same can probably be said of the psychotic states that occasionally occur.

The mental symptoms occurring with hyperfunction of the parathyroid glands have received little attention. They are seen in some cases of hyperparathyroidism. Fitz and Hallman (9) described two patients; one had paranoid delusions and confusion; the other complained at first of fatigue, insomnia and slow thinking for three months. Then he became confused, irritable with outbursts of temper and periods of boisterousness alternating with depression. Both of these patients recovered quickly and completely after removal of the parathyroid tu-

[1] This article has been adapted from an address given by Dr. Cobb on the occasion of the Dedication Exercises marking the opening of the Psychiatric Institute, University of Maryland.

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mor. Our experience at the Massachusetts General Hospital (8) is that many of the cases of hyperparathyroidism show headache and fatigability. A few become increasingly irritable and may become distressingly irascible. With this there may be a loss of the capacity to concentrate and to grasp a logical sequence of thought. At times this amounts to a confusion of ideas more noticed by relatives and friends than by the patient. After operative correction of the glandular overactivity, even the patients with severe mental disturbance were relieved and could again talk easily and carry logical arguments without effort.

After removal of parathyroid glands or tumors a rapid fall in the calcium content of the blood occurs and tetany may develop. With its onset the patients feel tense and tremulous. Later the neurological signs of tetany appear. In some cases the tense feeling may amount to anxiety and even panic. Calcium, given intravenously, often brings remarkable relief (1, 22).

The signs and symptoms of Cushing's Syndrome are due to hypersecretion of the adrenal cortical hormones. These may result from bilateral hyperplasia or tumor of one of the adrenal glands. Severe behavioral disorders are common but are often quickly relieved by operative removal of the offending adrenal cortical tissue. Depression is the most common symptom, often with agitation. Other symptoms observed have been panting attacks, panic states, tremor, palpitation, headaches, loss of libido, asthenia, memory defect, hypochondriacal delusions, visual and auditory hallucinations, feelings of guilt, inappropriate affect, ideas of persecution (23). In short, many patients show a depressed retarded state, others a schizophrenic syndrome, but usually the symptoms are mixed and may shift from one to the other extreme. There may be increased protein in the spinal fluid.

One might expect that the psychiatric symptoms found in Addison's disease (adrenocortical insufficiency) would by the opposite of those seen in Cushing's syndrome. But this is not the case. Some cases described have been strikingly similar (4). The disturbances seem to fall in the same schizo-affective group. It has been our experience at the Massachusetts General Hospital that the symptom of asthenia so dominates the picture that activity becomes minimum and mood and thought disturbances are expressed so little that they are easily overlooked. The psychiatrist is seldom called in and if he is, he must patiently observe if he is to uncover the psychiatric disturbances.

The psychoses of the latter part of pregnancy and especially those in the post-partum period, are often similar to those seen in Cushing's syndrome. Mild paranoid ideas usually appear first, sometimes followed by a mixture of schizophrenic and depressive symptoms. The disturbances are usually of only a few weeks' or months' duration, but they may last for years and end in schizophrenic deterioration. One can only speculate as to what may be the endocrine re-adjustments of the puerperium that accompany such psychoses. It is obvious that marked changes in pituitary, adrenal and ovarian secretions have recently taken place. The similarity to the psychoses of Cushing's and Addison's syndromes suggests the need of investigation in this area.

CLINICAL PICTURES INDUCED BY CORTISONE AND CORTICOTROPIN (ACTH)

Within the last few years a most important phenomenon has been observed. It has been found that giving cortisone or ACTH to patients suffering from medical ailments, and apparently normal mentally, has precipitated many of these patients into abnormal mental reactions, usually mild, but quite definite. It is impossible to say how many of the patients so treated show psychiatric symptoms, because the mild euphorias, anxieties and depressed states are easily overlooked and are not often recorded.

MINOR DISTURBANCES

Taking clinical impressions for what they may be worth, it is my impression that nearly all patients taking these drugs respond with euphoria and somewhat increased activity for a few days or weeks. In fact the sequence of events is so common that some physicians consider cortisone to be a "euphorogenic" drug and I am asked if it should be given to depressed patients. Unfortunately it has not proved beneficial in either reactive or essential depressions.

These mild reactions have been described in several papers, but most of the descriptions are brief. In a few reports the psychiatric descriptions are more adequate (5, 10, 11, 14). Lidz *et al.* carefully studied fifteen cases with severe medical illnesses (asthma, lupus, periarteritis and arthritis) who had been treated with cortisone and ACTH. Their most important conclusion is that these drugs do not cause transient degradation of mental function such as is seen in the "organic reaction types" or toxic psychosis. Twelve of their cases showed mild euphoria, but they considered it probably explainable by the amelioration of their medical symptoms. The only clear-cut elation appeared in a patient who had cerebral lesions related to periarteritis. From observation of a number of cases and perusal of available records the following picture may be drawn:

After cortisone or ACTH has been given to a patient in 50 or 100 milligram doses for two or three days, a common reaction is an increasing feeling of well-being, becoming a pathological euphoria in many instances. This is recognized by the patient's telling his physician how well he feels, by his labile mood and some restlessness and overactivity. Often the physician is less impressed by this than the family, who realize that the patient "is not himself." He may talk more than his wont; he may become more aggressive and "bossy." One patient expressed his euphoria by saying, "I could laugh all day long." But the labile mood may turn laughter into tears.

A beautiful description of the mood changes was given in verse by a talented arthritic patient as follows.

CORTISONE CONCERTO[3]

Opus Arthriticum for the Ill-Tempered Clavichord in Four Movements

I—*Allegretto grazioso:* (Admission to hospital)

How wonderful to have a bed
That really fits an aching back,
And to be waited on instead
Of struggling with my own hot pack.
How wonderful it is to know
The plumbing may erupt at home,
Yet I'll not have to plunge below
On crutches, tottering and slow,
And painfully the cellar comb
To diagnose the tidal flow.
How right (as usual!) is Chet
To think I need a little break.
I'll just relax, be good and get
As much from this as I can take;
And I'll obey him to the letter—
(By now, God knows, I've learned I'd better!)

II—*Andante cantabile quasi beatifico:* (Cortisone begins to work)

"Silent, upon a peak in Darien"—
So Keats described the wonder and the awe
Of him who traveled far, and climbed, and saw
The vast Pacific, never known to men.
So as I find that I can bend my knees,
So as my arms whirl smoothly overhead,
So as I find it doesn't hurt to sneeze,
So as I nimbly flip about the bed,
Above the future's shimmering expanse
Hope, like a rainbow in tomorrow's sky,
Flashes new freedom till the bright waves dance—
We'll *never* have arthritis by and by!

III—*Allegro molto agitato:* (A day or two later)

I'm tired of books and I'm tired of bed—
I wish for a change I could stand on my head.
I've hardly an ache and my progress is good
So why do I feel in this horrible mood?
My neck is supreme and my ankle is passable—
Why in the hell do I feel so irascible?
I've only to wait for one hip and a back,
So why do I feel as if stretched on the rack?
Keep your eye on the ball, you congenital dunce,
You're whizzing along, so stop crabbing at once.
I know—but with half of my brain I delight
In my luck—with the other half, I want to *bite*!

[3] Thanks are given to the patient and to Dr. Chester M. Jones for permission to publish this poem.

IV—*Presto accelerando furioso:* (The next day)

I'll bite my nails,
I'll claw my hair,
I'll *scream* at anyone who's there.
At the floor polisher's whine,
At all radios, including mine.
I shake
With jitters
And twitters.
I want to make
Sense. I can't—
Who cares? Not I—
I want to rant—
I want to cry.
I'm all hot,
All tied in a knot—
I *can't* face a lot
Of hours creeping
Without sleeping.
I hop
On top
Of my own skin—
I'll never get back in.
I itch
And twitch
Which
Makes me act like a bitch
And want to pitch
Into everyone—and how!
WOW!!

Less common symptoms following the giving of cortisone and ACTH are unreality feelings (depersonalization), depression and frontal paresthesias. The latter are quite typical: the forehead feels as if it were subjected to pressure, for example, "as if my hair were plastered down over my forehead." The terms "fullness, fogginess, dizziness" are used and referred to the frontal region.

These symptoms are often transient, but the euphoria may settle down into an improved sense of well-being that continues and gives satisfaction. It has often been argued that the euphoria is a normal reaction to the relief of medical symptoms; that one would expect to be made happy by losing the pain of arthritis or the obvious lesions of a skin disease. Against this theory are several facts. In the first place, careful observation of the patient usually shows that he is not just happy, but "slap-happy," with a push of speech and motor activity that is outside his normal habit. Secondly, the euphoria may appear before the improvement in medical symptoms. Finally, some patients are frightened by the euphoria; it makes them anxious; they are not happy (11).

Another syndrome of minor disturbance is likely to occur after prolonged treatment with cortisone or ACTH, when the drug is discontinued. This is somewhat the reverse of the syndrome seen at onset of treatment. Two or three days after cessation of the medication, the patient may become apathetic and anxious; feelings of weakness of the limbs and heaviness of the head are common complaints. The patient feels tense and unpleasantly restless. The mood is depressed and suicidal thoughts may occur, especially if the medical symptoms return after a period of relief. Like the minor reactions at the onset of therapy, these reactions are usually transitory, lasting from a few days to a week or two.

It seems from this description that the minor disturbances are largely in the sphere of mood and activity; they resemble mild manic or depressive reactions. The only symptoms that could be considered at all schizoid are the feelings of unreality and perhaps the tense feelings and the somatic complaints.

In summary, it may be said tentatively that a common picture of the mild reaction consists of an initial period of a few days, when the drug is started, in which the patient shows euphoria, restlessness, feelings of unreality and frontal paresthesias. These gradually pass off, to be followed by a mild depressive reaction for a few days when the drug is discontinued. The patient is anxious and apathetic; he feels weak and depressed; sometimes he is anxious and tense. Frequently there is a feeling of heaviness in the head. This reaction is brief; a week or ten days after stopping the drug he usually is psychologically normal unless medical symptoms have returned to discourage and frighten him.

MAJOR DISTURBANCES

The major disturbances, or severe psychiatric reactions, have been better described

in the medical literature (5, 10, 21). A group of 22 cases has been carefully observed by us at the Massachusetts General Hospital, and 12 other adequately observed cases from published papers have been added. All 34 have been analyzed and a chart of the symptoms has been constructed (Figure 1). The most common symptoms are at the top, and the symptoms are listed in descending order of incidence. The figures are only approximate, and no great accuracy can be claimed for the chart, but it gives a picture of the great variety of symptoms seen with an indication of how often they occur.

The symptoms of an agitated depression are the commonest, but the schizophrenic symptoms of persecutory delusions, hallucinations, concern with the body, depersonalization and bizarre behavior are well mixed in near the top of the list. A few of the worst cases had periods of frank mania. Variability is the rule, the symptoms changing from day to day.

A list such as that given in Figure 1 can give no picture of the individual case and its clinical course. Such descriptions may be found in the clinical papers referred to (5, 10, 21).

Comparing the psychiatric symptomatology of Cushing's syndrome with that seen in the cortisone and ACTH reaction, it is seen that the Cushing's cases as a rule have milder reactions with depression, showing retardation and lethargy—a more common picture. There is less restlessness and agitation. The patients with Cushing's complain more of asthenia, and often have anxiety, but we saw obvious agitation in only three cases. Emotional lability and irritability are common. Persecutory ideas, hallucinations and delusions occurred definitely in about a quarter of the patients, but the schizophrenic elements, although present in the severe cases, were not as conspicuous as in the ACTH and cortisone reactions. Insomnia, a frequently mentioned symptom in this group, was not observed in the Cushing's cases. Manic hyperactivity was only seen in three of the patients with Cushing's syndrome.

FIG. 1. Presenting psychiatric symptoms in 34 cases of reaction following medication with cortisone and ACTH.

It is difficult to draw any typical picture of the severe cortisone reaction because it is typified by variability as much as anything else. One may perhaps draw the following picture of a common type of severe reaction: A few days after taking cortisone the patient begins to be euphoric and restless; next day he is frankly manic, talkative and a nuisance on the ward. Taken to a protected room he becomes suspicious, finally expressing strong persecutory delusions and feelings of unreality. His behavior becomes bizarre; he may become mute and ritualistic. This phase may be followed by severe depression, which gradually clears and may end with a few days of slightly manic behavior. The course of such an illness might take two to four weeks. Our longest case continued these changes from manic picture

to schizophrenic to depressed, and back with various mixed states, for three and a half months. One man, who had been through several manic-depressive psychoses in former years, was given ACTH for a metabolic disorder and promptly developed a mixture of manic and paranoid behavior which necessitated commitment for over a year.

SOME SPECULATION ON THE MEANING OF THESE OBSERVATIONS FOR AN UNDERSTANDING OF SCHIZOPHRENIC AND MANIC-DEPRESSIVE (SCHIZO-AFFECTIVE) DISORDERS

Far be it from me to start a discussion as to whether schizophrenia is a "physical disease or a mental disorder," whether it is "hereditary or environmental," "organic or functional." Anyone who has followed the development of genetics and psychosomatic medicine in the last twenty-five years should know that such questions are anachronistic and as dead as the Great Auk (7). What one inherits in his specific genes is a tendency to organization along certain lines (12). During development these tendencies are abetted or blocked by thousands of processes going on in him and in his environment. The varied processes may arise from such different causes as the health of his mother during his gestation, the amount of iodine in his drinking water, or his emotional relations with his parents. Questions posed as biological problems in the form of "either-or" are usually silly. The problems are too complex. The mature human individual (phenotype) is the resultant of the innumerable impacts of his internal and external environments upon what he was given by heredity (genotype). It is never a question of *either* heredity *or*

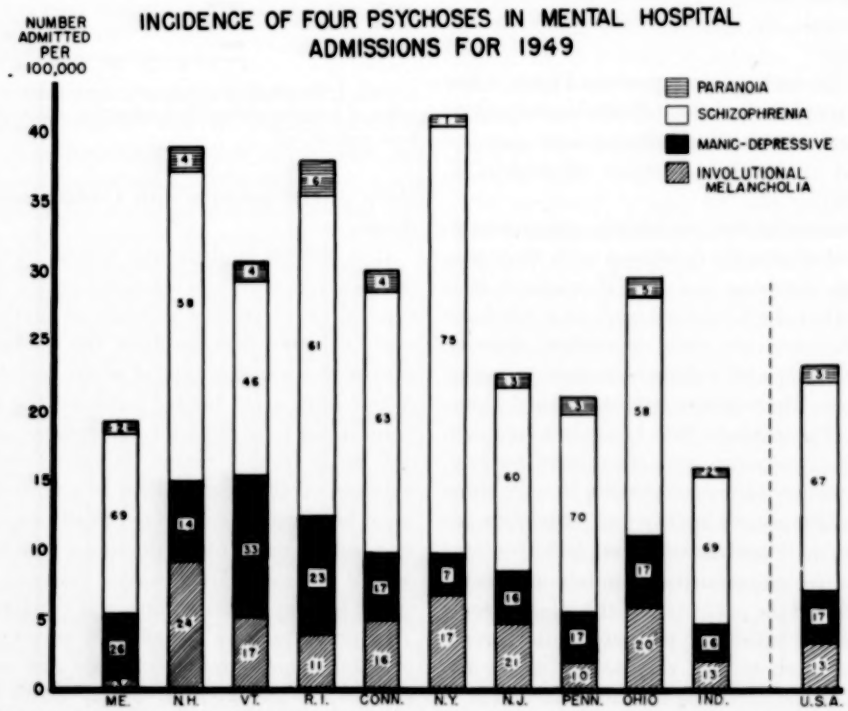

FIG. 2. Incidence of four psychoses in mental hospital admissions for 1949. These data were taken from tables in *Patients in Mental Institutions*, a publication of the Federal Security Agency (24). The figures on the ordinate are in numbers of admissions per 100,000 population. The numbers within the bars are percentages of admissions for each diagnosis within each state.

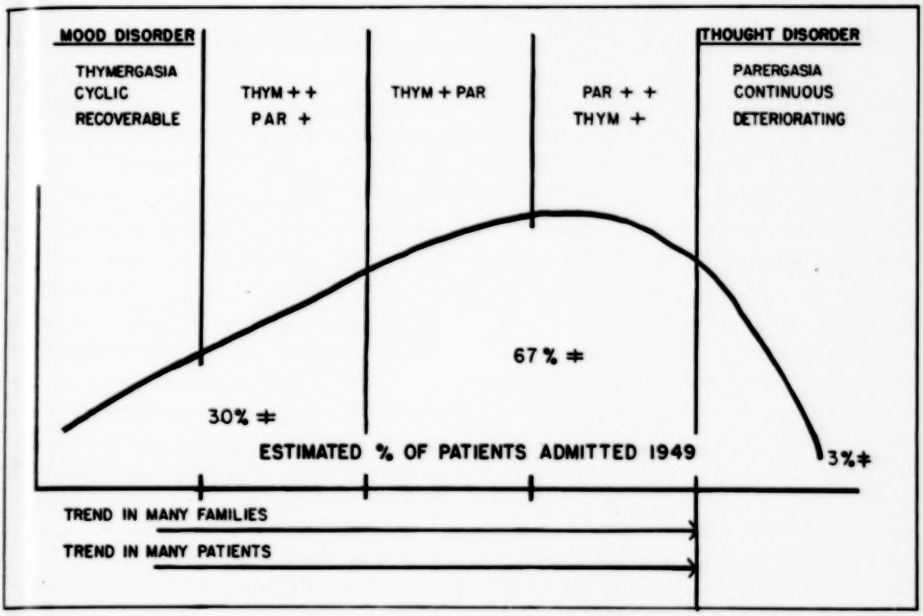

FIG. 3. Curve made from data in Figure 2, to show the probable incidence within the "schizo-affective group" of "pure manic depressive" reactions (left-hand column) and mixed reactions (three middle columns). The data are inadequate, so the curve must be looked upon as a tentative first approximation. The two extremes are described as "mood disorders" and "thought disorders" as representing the essential psychopathology of "manic-depressive psychosis" and "schizophrenia," respectively. Meyer's (16) terms *thymergasia* and *parergasia* are used as good expressions for the disorders: "thym" indicating mood, and "par" indicating thought disorder. The varied mixtures of these are indicated in the middle three columns. Thymergasia is more cyclic and recoverable; parergasia is more continuous and deteriorating. The two arrows below suggest that there is also a tendency in manic-depressive families to produce schizophrenic offspring in later generations. In individual patients manic-depressive attacks may develop into schizophrenia (see text).

environment being responsible; it is a question of how much one develops and influences the other.

THE CONCEPT OF THE SCHIZO-AFFECTIVE GROUP OF MENTAL DISORDERS

Much time has been spent in staff meetings deciding whether to label a given patient "manic-depressive psychosis," "involutional melancholia," "paranoia" or "dementia praecox" (schizophrenia) (see Figure 2); much argument could have been saved if it could have been realized that there are no dividing lines between these four. Elkind and Doering showed in 1928 (quoted by Gruenberg, 17) that the variations in diagnosis from hospital to hospital were so great as to make very questionable the significance of the two categories. Gruenberg (17) substantiated this in 1950. If all cases could be plotted on a curve with "pure" manic-depressive at the left and "pure" dementia praecox at the right, I believe that there would be few cases at the extremes and many in the middle (Figure 3). That is to say, there are more cases that show a mixture of manic-depressive and schizophrenic symptoms than there are "pure" cases of either.

If typical mood disturbances, that tend to be cyclic and reversible, are put on the left side of the chart, and if disorders of thought content, that are continuous and tend to lead to deterioration, are put on the right of the chart, it will be seen that the incidence of the former is in general less than that of the latter. In the United States "schizo-

phrenia" plus "paranoia" were diagnosed in 1949 on 23,193 first admissions, whereas "manic-depressive" and "involutional" added up to 10,172 (24). When these figures are taken by states as well as for the whole Unites States and reduced to rates per 100,000 (see Figure 2), it is seen that the data give some justification for making such a curve as is shown in Figure 3. The highest point on the curve of incidence is for mixed psychoses, such as "paranoid schizophrenia," about four times as common as typical mood disorders ("pure manic-depressive") and about 20 times as common as "paranoia" which could be taken to typify "pure thought disorder." The involutional psychoses are typically mixtures of mood and thought disturbance, so help to build up the curve to the right of the center. No data are available that indicate the incidence of the various mixed psychoses, but clinical experience suggests that the line as drawn in Figure 3 might be taken as a first approximation.

If we combine all four diagnoses to make one group and call them, for want of a better and shorter name, the "schizo-affective disorders"[4] the broad description of the group would be that it is composed of *persons largely 15 to 65 years of age who are committed to mental hospitals because of disorders of mood and thought, who have no demonstrable cerebral or somatic lesions or intoxication.* It is a large group. It accounts for about 23 first admissions to the mental hospitals of the United States per 100,000 population per annum (Figure 2). This figure varies in the different states, but the internal structure of the group is fairly consistent, being approximately: schizophrenia, 67 per cent; manic-depressive, 17 per cent; involutional, 13 per cent; and paranoia, three per cent. The variations are shown in Figure 2. The greatest variation is seen in the diagnosis of "involutional"; it varies in the year shown from about three per cent in Maine to 23 per cent in New Hampshire! Crossing the state line cannot make that biological difference; it seems highly probable that the criteria for diagnosis used by the staff of the state hospital in Maine differ significantly from those used in New Hampshire. In Massachusetts, a nearby state with 13 state hospitals, the figure was near 17 per cent and in New York, 16.8 per cent. These figures are intermediate and suggest that several staffs pooling their diagnoses yield more agreement. In most states where a high number of "involutional" diagnoses are made, the number of "manic-depressives" is low. "Schizophrenia" varies less, but the extremes are wide apart—46 per cent to 75 per cent. The paranoias always form a small group.

Why this great variation in diagnosis? One explanation could be that psychiatrists are trying to separate (by inexact criteria) groups that are not separable. Instead, they should be trying to pick points on a curve that represent variable phenomena in one broad type of abnormal human reaction. If the disorder is mostly in mood the course tends to be self-limited or cyclic and the cases go to the left end of the curve (see Figure 3) near the rare "pure" mood disorders; if the disorder is mostly in content of thought, it tends to be less cyclic and more likely to lead to progressive deterioration. This puts the case towards the right of the curve, nearer the "pure" thought disorders. Most cases fall between with variations of all degrees. The curve, however, is skewed, because there are more than twice as many admissions for thought disorders (schizophrenia plus paranoia) as there are for mood disorders ("affective psychosis," "manic-depressive" plus "involutional"). In 1949 for

[4] "Schizo-affective" is used as a generic term, including manic-depressive, involutional, schizophrenic and paranoid conditions. Perhaps in medicine we should think more of genera combining species and subspecies. A more euphonious term for this genus might be "Parathymic," a composite word taken from Meyer's "parergasia" plus his "thymergasia" (see Figure 3). Or we might simply take the word "psychosis" and restrict its use to this group of mental disorders. In fact, many psychiatrists already use "psychosis" in that sense. The term "functional psychosis" is, of course, illogical and indefensible on any grounds (6).

the whole United States the rate of first admissions was about 70 per cent as compared to 30 per cent. My guess would be that perhaps five to 10 per cent of the whole would be patients with nearly "pure" mood disturbances, while three per cent represent the paranoias at the other end, which could be looked on as a practically "pure" thought disturbance.

There is nothing new about this concept. Adolph Meyer taught me at the bedside in 1917 that the mixed cases were common and that the more they showed cyclic mood changes the better was the prognosis and vice versa. He evidently thought of them as related types of reaction (16). Another important observation made by many psychiatrists who have watched patients over long periods, is that a patient may have a first attack of psychosis that is typically manic or depressive, with no noticeable schizophrenic features; later, in subsequent attacks, schizophrenic symptoms appear and become more prominent, until the patient is permanently hospitalized with a typical deteriorating schizophrenic picture. This clinical impression is substantiated by Elkind's figures (17). Mulvaney has recently stated (18):

"Pure psychotic reactions corresponding to the classical types are not so common as those with mixed features and the manic-depressive and schizophrenic groups do not represent mutually exclusive categories but seem to form a continuum, and today we have the legacy of this at clinical meetings, when an argument ensues as to whether the patient is suffering from paranoia with depression or from depression with paranoia. A far more practical approach is to accept the mixture and evaluate its varying components for the purposes of treatment and prognosis. Hence, pursuing genetic studies in the hope of finding the psychosis "breeding pure" may be a waste of time. Schultz suspects that there are genetic factors common to both the schizophrenic and affective disorders, and some of his studies confirm this. Thus there may be a common etiological factor in the major psychoses, the difference in symptomatology being due to the reactions of varying constitutions and other factors, such as the age of onset. Patients with a lifelong psychosis have been known to show manic-depressive and schizophrenic features."

It not only happens in individual patients that an affective psychosis may gradually change into a schizophrenic, but there is evidence that it also happens in heredity. Myerson (19) has pointed out that both disorders run in certain families quite strongly and that the general tendency is for a family to begin with manic-depressive cases and after a few generations to have the offspring more and more often turn out to be schizophrenic. This may finish the family because schizophrenic patients are poor breeders. Kallmann (13) does not agree with Myerson and believes that inheritance in manic-depressive psychosis differs from the type found in schizophrenia. Even if he is right concerning the "typical" cases at the extremes of the curve, the mixed cases probably have mixed forms of inheritance. The terms "dominant" and "recessive" are not mutually exclusive.

I do not believe that manic-depressive psychosis and schizophrenia are due entirely, or even largely, to heredity. The tendency to breakdown certainly runs much more strongly in some families than in others; in some the hereditary tendency is so strong as to be probably inescapable. In others it takes much environmental stress to bring on the reaction. Probably in all persons there is a cyclic mood swing of some degree and a tendency at times to distorted primitive thinking. The good or bad fortune of psychological and other environmental precipitants is almost certainly of major importance in each case.

The main object of this paper is to emphasize these well-known concepts again and to bring them into relation with the new facts observed in patients with endocrine

disturbances, especially the recent observations on mental reactions following cortisone and ACTH medication. These patients in a brief space of time may show all the symptoms of the schizo-affective group of psychoses from euphoria through depression to catatonia, and back again with variations. This suggests to me that the endocrine glands play a great role in determining human behavior; that both heredity and environment are important; and that endocrine function is important in determining the development of parathymic (schizo-affective) psychosis. Active research should immediately be aimed at elucidating the origin of the various hormones, their mode of transmission to target tissues and the variations in absorption by, and effect on, these tissues. Only when these different combinations of function can be measured and related to behavior of the organism can the psychiatric problem be solved.

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FETISHISM: A STUDY OF ITS PSYCHOPATHOLOGY WITH PARTICULAR REFERENCE TO A PROPOSED DISORDER IN BRAIN MECHANISMS AS AN ETIOLOGICAL FACTOR

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The cause and nature of the psychic disturbances encountered in fetishism have eluded a comprehensive explanation. Modern inquiry into this disorder, which has employed primarily psychoanalytic techniques, has investigated and helped clarify both the psychodynamics of the fetishist and the symbolic significance of his fetish. However, there has not been as concerted an attempt to explore those unique characteristics of the fetishist from which spring not only the intense affect accompanying his drive toward an inanimate object but also, almost invariably, other associated and equally striking behavioral abnormalities.

Some abnormalities, for example, displayed by a shoe fetishist treated by the author, included: 1) sudden transitory feelings of fear and depression, apparently unrelated to specific thought content; 2) an imperative urge to perform certain motor acts; 3) occasional forced thinking; 4) marked readiness of sexual arousal by the fetish object; 5) great ease and frequency of ejaculation; 6) sexual arousal by feeling states ordinarily non-erotic, for example, the state of fear; 7) vivid mutilation dreams; 8) a general over-evaluation of the significance of symbols.

Do similar, and perhaps additional related phenomena exist in other fetishists? If so, what is the nature of such phenomena? An attempt to answer the first question requires a review of the clinical data available in the literature. An approach to the second may be afforded by the recent report of Mitchell, Falconer and Hill (23) of a fetishist whose fetish, a safety pin, eventually became associated with epileptic attacks of the psychomotor type. Diagnostic procedures having revealed an abnormality in the left temporal lobe in this case, a temporal lobectomy was performed which resulted in the disappearance of both the patient's desire for a safety pin and his seizures.

Dysfunction of the temporal lobe and its sub-cortical connections is currently a subject of extensive investigation. Recent studies have thoroughly described temporal lobe seizures, and some have explored their psychodynamic significance (7, 16, 26, 29, 31). Other studies (8, 15) have shown a high incidence of psychiatric disturbance in both epileptic and non-epileptic patients with temporal electroencephalographic abnormalities, and it has also been noted that this group of patients display varied forms of abnormal episodic behavior including acute psychotic states (8, 15). Further, by means of depth electrodes, a correlation has been demonstrated between recording abnormalities, in the septal region, rostral hippocampus and amygdala, and pathological behavior in patients with episodic behavioral disorders (13).

It is the purpose of this study to describe certain characteristic behavioral phenomena encountered in fetishists, to examine the relationship between some of these phenomena and those of brain, particularly temporal lobe dysfunction, and finally to propose a theory of fetishism.

In addition to the author's case, the material for this study is derived from 10 well-documented case studies in the literature (1, 4, 10, 11, 17, 23, 27, 28, 32, 33), and from the case excerpts collected by Krafft-Ebing (20). (The present study is confined to cases in which the fetish is an inanimate object;

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not a part of the body.) The first part of this paper will be primarily devoted to presentation of data while, in the last portion, the data will be interpreted and theoretical considerations advanced.

CERTAIN CHARACTERISTIC BEHAVIORAL PHENOMENA IN FETISHISM

Analysis of the case material of fetishism reveals a number of characteristic behavioral phenomena. These will be described under the following six headings: 1) Some Character Traits and Historical Features; 2) The Fetish Object; 3) Orgastic Behavior; 4) Episodic Behavior (including epileptic and acute psychotic states); 5) Omnipotence of Symbols and Thought; 6) Fantasies, Dreams and Disturbances During Sleep.

SOME CHARACTER TRAITS AND HISTORICAL FEATURES

Fetishism appears to occur predominately in men. The fetishist is usually reserved and nonassertive in manner, displaying little spontaneity or warmth of emotion. He generally presents a constellation of character traits of the obsessive-compulsive variety, but occasionally qualities of passivity and dependency are in the forefront. There is an intense inner preoccupation with the fetish and a strong fantasy life of sterotyped content. Sexual fears are so marked that intercourse is completely avoided when possible or, if indulged in, is rarely pleasurable. Romantic attachments may occur, and their disruption may produce feelings of depression. The fetishist has marked fears of body mutilation which may be expressed as phobic or hypochondriacal symptoms.

A review of the early histories of fetishists reveals, as a consistent finding, a marked attachment to the mother; often an unusual physical closeness. There is a suggestion of precocious sexuality manifested primarily by self-stimulation. Another frequent finding is the presence of frank sadistic behavior, for example, the torturing of animals. This behavior generally disappears during adolescence, but the content of later fantasies contains much sado-masochistic material.

THE FETISH OBJECT

The fetish object is manifold and may include such varied articles as a shoe, glove, uniform, mackintosh, apron, safety pin, or automobile exhaust pipe. The fetishist usually requires that his object have very specific qualities in the absence of which its desirability is lost, for example, an exact shape or color, or a particular attribute as wetness or dirtiness. The fetish excites through stimulation of any of the senses, and, by means of it, ejaculation may be achieved through use of any of the body parts; the fetish may be smelled, sucked, chewed, rubbed with the penis, placed over the skin, or manipulated with the hands or feet.

The image of the fetish may appear in consciousness as the result of volitional fantasy, or spontaneously and involuntarily. The fetish frequently dominates waking life either through its presence in fantasy, its involuntary appearance in awareness, or when its actual physical presence is demanded to reduce tension. Similarly, the fetish makes a frequent appearance in dreams, which are then often accompanied by seminal emissions. Although the fetish reduces tension, the satisfaction so gained is momentary. Feelings of marked tension quickly return, accompanied by the irresistible need of the fetishist to possess again his fetish object. Despite these painful aspects of fetishism, it is almost impossible for the fetishist to voluntarily abandon his fetish object.

ORGASTIC BEHAVIOR

Usually, the fetishist achieves orgasm only with the aid of the fetish. Self-stimulation is the preferred method and may be performed many times daily. It is striking, however, that ejaculation often occurs at the mere sight or fantasied appearance of the fetish; or by simply touching it or otherwise

gaining contact, without direct physical stimulation of the genitals. Indeed, the threshold for ejaculation in the fetishist may be so easily reached that, at times, merely the prospect of attaining some contact with the fetish suffices. For example, the shoe fetishist studied by Grant (11) stated, "Often I have boarded trains in pursuit of a woman wearing my fetish. Sometimes the starting whistle of the engine would induce ejaculation." He ran beside trains and "had ejaculations while running at almost top speed."

Ejaculation may be so easily elicited that it may occur when a normally non-erogenous area is stimulated. In addition, genital excitation may be produced by physical stimuli or by emotions which are not clearly erotic. For example, one patient (33) would "frequently break bottles, pots and other fragile objects and get a tickling sensation in the urethra." He would also note a similar sensation in the penis when the dentist would drill his teeth. Another patient (2) would become sexually excited when in a physically dangerous situation, and, in adolescence, dreams, in which he was in a state of fear, were accompanied by seminal emissions. Similarly, a third patient (20) had nocturnal emissions during dreams in which he became "anxiously excited."

The mouth and gastro-intestinal system are also highly responsive to sexual or other stimuli. The effect on Gillespie's patient (10), a uniform fetishist, of a woman in a uniform was self-stimulation and orgasm, but one not in a uniform would make "his mouth water, his teeth gnash, and he wants to eat her up." Several times, during psychotherapeutic sessions, he experienced "excitement felt largely in the mouth and combined with fantasies of nurses in white, stiff, crackly uniforms." This patient also had a "mass peristalsis" when excited over the thought that a girl had "rung" for him.

The gastro-intestinal system may react almost automatically to stimuli which are symbolic or which gain their strength by displacement. For example, Payne (27) writes of a patient who collected books and "always wanted to defecate when he entered a book-shop." On one occasion, another patient (32) saw a butcher wagon and had to "fight himself to keep from vomiting."

EPISODIC BEHAVIOR

The term, "episodic behavior," as used in this study, includes frank epileptic and acute psychotic states as well as "episodic symptoms" (disturbances in perception, affect, ideation, motor and visceral function which appear suddenly and involuntarily; they are self-limited and not epileptic in the conventional sense) (8).

a) *Epilepsy:* Mitchell, Falconer and Hill, (23) and Krafft-Ebing (20) have described frank epileptic seizures in fetishists.

The subject of the formers' case study was a man, thirty-eight years of age, whose fetish was a safety pin. The relationship between the fetish object and the subsequent development of seizures is of interest. For as long as he could remember, the patient had a "thought satisfaction" when looking at a safety pin. Between the age of eight to eleven years, the "thought satisfaction" began "to be followed by a blank period." In his twenties, the seizures became more complex: "The patient would stare at the pin for a minute and then appear glassy-eyed. Next he would make a humming noise for a few seconds and for a few further seconds sucking movements with his lips. Finally he stood immobile and unresponsive for two minutes. Recovery was then immediate." By the age of thirty-one years, the period of immobility was followed by motor automatisms and also by brief periods of post-ictal confusion, during some of which the patient would dress himself in his wife's clothing.

A fit would only occur when the safety pin served as a stimulus either through its actual presence or through its fantasied appearance. The safety pin was a true fetish providing the patient with his only true source of sexual gratification.

Another example of the precipitation of

seizures by the fetish object is described by Krafft-Ebing. This patient was a shoe fetishist who had convulsions in infancy. No mention is made of further seizures until later in life when he opened a shop in which shoes were among the articles sold. "He was excited sexually by fitting shoes for his female patrons, or by manipulating shoes that came for mending. One day while doing this, he had an epileptic attack and, soon after, another while practicing onanism in his customary way." The patient attempted to overcome his seizures by refraining from selling shoes, but "then frequent pollutions, with erotic dreams about shoes occurred, and the epileptic attacks continued."

Of related interest in reviewing Krafft-Ebing's case material is that two other of his fetishists had childhood convulsions.

b) *"Episodic Symptoms":*

Visual Phenomena: In addition to the image of the fetish object, other spontaneous visual images and scenes may suddenly enter awareness. These may resemble screen memories and occasionally have a hallucinatory quality. They are differentiated from the visual fantasies, commonly found in fetishism, by their involuntary nature. Episodic perceptual disturbances in fetishism appear to occur primarily in the visual sphere, no examples of the auditory variety having been encountered.

As example of the spontaneous appearance of a visual image followed by an alteration in consciousness and then by feelings of visual distortion is described by Stekel (33) in his case of orthopedic-appliance fetishism. During psychotherapy, while associating to a dream, this patient suddenly "sees an old picture: his mother in a black dress and a black funeral hat. In his moment he goes off into a peculiar mental state, a sort of trance." Then, "he begins to feel as if space were limitless and that he is in an infinitely wide and broad room. His legs become longer and longer, his arms are stretched immensely ... everything seems to be far off and away ... I and everything in the room appear to him as if he were looking through the wrong end of an opera glass: very small and far away." Stekel remarks that this patient had complained of micropsia and macropsia, as well as of "trance states," when he was a boy.

In Abraham's patient (1), a shoe and corset fetishist, "certain obsessive ideas" would appear if the patient were to think of early childhood. One was "a scene at a seaside resort, in which he saw his mother wading into the water." It is of interest that another of the patient's "obsessive ideas" was "the smell of iodoform and pyroxylic acid" which had both been used by his mother in his childhood. Payne's patient (27), whose fetish was a mackintosh, at the age of four "had an hallucination ... of seeing a man and woman kissing in a hedge where he and his brother used to urinate. The picture was in a flood of light."

Affective Alterations: Episodic affective changes, besides those generated by the fetish object, are commonly found in fetishism. These are primarily spontaneous feelings of depression, fear or rage which often arise in an isolated fashion without apparent relation to specific thought content.

The author's patient (2) had frequent brief attacks of anxiety, which presented themselves without apparent relation to specific ideation but which could often be linked to fears of sexual intercourse. On several occasions this patient awoke from a dreamless sleep feeling "panicked." There were also many brief episodes of depression whose cause at times eluded explanation; but no episodic rage. Stekel's orthopedic-appliance fetishist would also awaken at night in a state of "frightful anxiety" which would almost invariably be preceded by a dream in which he saw a nondescript but gradually enlarging threatening object.

The feelings of intense rage which occurred in Bergman's patient (4), whose fetish was an automobile exhaust pipe, are described as follows. "His pent-up aggressions at times reached such heights that he felt if someone

so much as called him by name, he, the patient, might bite into the person's throat." Both Stekel's orthopedic-appliance and apron fetishists (32) were given to fits of anger, the latter having once "fallen upon his sister with a butcher knife" wanting to stab her. In Hunter's case of mackintosh fetishism (17), intense rage outbursts were frequent; spontaneous feelings of depression also emerged.

Krafft-Ebing (20) has also described affective changes, of an apparent episodic nature, in his case data. For example, a night-cap fetishist, since childhood, "had been subject to occasional attacks of depression, with tendency to suicide, and now and then to frightful hallucinations at night" . . . while, in a handkerchief fetishist, "frequently a depressed anxious state of mind came over him."

Ideation: Although perhaps more conventionally viewed as another example of obsessive thinking, which is almost invariably present in fetishism, the sudden and involuntary appearance of thought or thought-fragments in consciousness, occuring in some fetishists, may be regarded as an episodic symptom.

This phenomenon was particularly evident in Stekel's case of apron fetishism. This patient had attacks in which, having awakened from sleep, troubled by an oppressive sensation in the chest and by some difficulty in breathing, he "could not dispel the thoughts of a few harmless occurrences of the day before" from his mind. During a coughing seizure he must think repeatedly, "They're all forgotten!" On one occasion, he "had an obsession on the number 1889 and had to keep repeating it over and over." Stekel also noted, "In dreams . . . the word Ariel seemed to dog him obsessionally." In his case study, Stekel explores the psychodynamic significance of these thought-fragments.

In the author's case, the patient occasionally noted that thoughts, which seemed foreign to him, would suddenly "pop" into his mind, unaccompanied by affective charge.

Motor Function: Forced episodic motor symptoms, ranging from simple to complex acts, have been noted in some fetishists. An example of an unpatterned act occurred in the author's patient who reported several episodes in which he experienced an ill-defined "ticklish" feeling in the feet, associated with a compulsion to move them. He gave the following description: "I had to move my feet. I couldn't stop doing it; my muscles felt like twitching." In one of these attacks, the movements persisted for about thirty minutes. Perhaps a related phenomenon is the sensation the patient reported one day of a need to do everything quickly. Accordingly, he performed all his activities of that day in a hurried manner.

A more patterned motor act occurred in Stekel's orthopedic-appliance fetishist who had episodes of transformation of his facial expression. During these periods his "usual friendly face" assumed a threatening appearance which could not be altered. Stekel comments, "It is like a compulsive state which will not liberate him."

Krafft-Ebing reports two cases in which complex and automatic behavior, related to the fetish object, occurred in a state of altered consciousness. In the first, the patient, a shoe fetishist, had severe attacks of headache associated with a "peculiar impulse to take the shoes of female members of the family—as a rule only one at a time—and hide them in some out-of-the-way corner." The patient was amnesic for these episodes. In the second case, that of a handkerchief fetishist, the patient, while in an altered state of consciousness, would wipe his face with a handkerchief. This act was accompanied by erection and occasionally ejaculation.

c) *Acute Psychotic States:* Acute, transitory, psychotic episodes have been frequently described in fetishists.

Mitchell, Falconer, and Hill record three psychotic episodes in their patient, two of which followed seizures. During these epi-

sodes, which were of two to three days' duration, the patient was "grandiose, paranoid and loudly religiose" claiming on various occasions that he had discovered a cure for cancer and that he had received messages from God.

Bergman's patient had a "short break with reality" of less than one day's duration in which he experienced hallucinations of "terrible witchlike women" torturing him.

Peabody, Rowe and Wall (28) report an acute psychotic reaction lasting for eighteen days in a glove fetishist. It is stated that the onset of this reaction was related to an intensive "self-analysis" undertaken by the patient in an effort to abandon his fetish. The psychosis was "characterized" by episodes of tension and panic interspersed with periods of ecstatic, bizarre behavior." While psychotic, the patient "felt impelled to assume fetal postures and to play with feces."

Of related interest is the reaction which occurred in Stekel's orthopedic-appliance fetishist, who, while in church, developed "a sudden rush of delusional grandeur. He seemed to himself to have swollen to such imposing proportions as to fill the entire cathedral."

Mention should also be made of Hunter's patient who, at one point during his psychoanalysis, developed "rapidly mounting persecutory anxiety," followed by a "chaotic period of about three months" and of Gillespie's patient who was referred for treatment because of "a very severe reaction taking the form of a hypochondriacal depression."

OMNIPOTENCE OF SYMBOLS AND THOUGHT

The life of the fetishist is dominated by a symbol, the fetish. But in addition, other symbols and thought itself assume great and magical power, primarily serving as sanctions and prohibitions in a fashion similar to that encountered in the obsessive-compulsive reactions. For example, a shoe fetishist (2) would find it uncomfortable and difficult to fantasy himself having sexual intercourse, but could do so with greater ease, if, in the fantasy, his partner would be visualized as wearing a wedding ring. Another patient (27) could not use a camera because of the magical power imputed to it, while still another (32) could not write the letter *L* in combination with the letter *D*. Gillespie's patient feared to kiss his girlfriend excessively because "he felt that kissing her meant eating her up."

Simple compulsive acts and rituals are also frequent. As an example, one patient (33) was "impelled to call out a certain doggerel thirty times in a row."

FANTASIES, DREAMS AND DISTURBANCES DURING SLEEP

The fetishist is often preoccupied with fantasies, which are characterized by a stereotypy of content and by a tendency to be acted out. The fetish object plays a dominant role in the fantasies. A common type of fantasy is one in which the fetishist, while standing before a mirror, puts on or otherwise places his body in contact with his fetish, and, at the same time, imagines himself the natural possessor of the object, for example, putting on a woman's shoe and fantasying himself as a woman. But employing the fetish in this fashion, to express the wish to fuse or identify with a woman, does not complete the roles which it may play in fantasy life. For example, the automobile exhaust pipe fetishist, studied by Bergman, masturbated while fantasying the fumes from the pipe "blackening some white object" or while imagining himself sucking exhaust pipes. In other fantasies, "the exhaust was pushed into his mouth (or a baby's mouth) and the helpless victim was killed by the poisonous gases;" the exhaust was used as a "weapon against a woman's breast, burning and torturing her"; or the exhaust was "boring a hole into the patient's pants, blowing against his buttocks." Such a condensation of meaning in the fetish was emphasized by Stekel and has subsequently been noted by other authors.

An almost invariable theme in the fetish-

ist's fantasies is that of sado-masochism. In the masochistic fantasies, which he may carry out on his own person occasionally to the point of physical danger, the fetishist imagines himself being whipped, bound, tortured and at times compelled to submit to homosexual intercourse. An interesting variant of such masochistic fantasies is that described by Abraham in his patient, who "had all his life-long indulged in fantasies in which he was forced to refrain from relieving his needs. For instance, he would like to imagine that he was tied to a stake by Indians and compelled to hold back the contents of his bladder and bowels." The sadistic fantasies, rarely acted out, often have as their content, the wish to mutilate a woman's body.

The manifest dream content of fetishists has at least one other common characteristic, besides the recurrent appearance of the fetish object; dreams in which the dreamer is being attacked or mutilated. In such dreams, the castration motif is often revealed without disguise; the penis being pictured as bleeding, crushed or otherwise wounded. Vivid mutilation dreams may be present in childhood—for example, a recurrent dream, occurring at about the age of nine, in a shoe fetishist (2) had the following content: "A nurse would come and pour boiling water on boys' heads. It would make a hole in the head. Once this happened to me."

Although Stekel commented that every one of his fetishists had been an enuretic, this symptom does not seem at all invariable. However, it has been noted in cases studied by other authors (11, 20, 28). Other disturbances in sleep described in fetishists include: somnambulism (27), transient somnambulism in youth (33), and persistent nightmares of life-long duration (11).

COMMENT

ORGANISMIC EXCITABILITY AND ATTEMPTS AT CONTROL

Is there a pattern or common unifying qualities in the phenomena just described? In trying to discern such a pattern, it appears possible to group the phenomena into two broad categories: the first consisting of those representing a state of increased organismic excitability or, from another point of view, a failure in organismic control;[2] the second, representing defenses which arise in an attempt to secure control. The phenomena may also be intermediate between these two poles, containing elements of both.

The state of increased organismic excitability may be defined as one in which the total organism reacts excessively to stimulation. Responses then tend to be extreme in degree and diffuse; they cannot be properly integrated. As manifestations of this state, one may include marked responsiveness of the genitals and alimentary tract (to symbolic as well as physical stimuli); sleep disturbances with unusually vivid dreams; and episodic behavior, ranging from the relatively uncomplex through frank epileptic states and culminating in acute psychotic reactions.

The defenses which develop because of the need to secure control include compulsions, obsessive thought processes and the facade of emotional reserve. Further, the masochistic fantasies, particularly those involving binding or other methods of restricting motor or visceral action, may, as part of their meaning, symbolize the fetishist's struggle to inhibit the expression of the underlying excitable state.

The fetish object seems to represent a resultant of both the forces of excitability and control. Its spontaneous and involuntary appearance in awareness and its dominating "driving power" are characteristics of dyscontrol. On the other hand, the fetish provides control by serving as the focus toward which basic drives, particularly the sexual and aggressive, are directed and consummated. The fetish absorbs these drives and

[2] Menninger and Mayman (22) have adopted the term "episodic dyscontrol" to include a wide range of disorders with episodic symptoms, primarily impulsive aggressive behavior.

prevents their explosion on animate objects. Thus the fetish may be viewed as a "symbolic binder."

The classification of the behavioral phenomena of fetishism into two apparently polar categories is partially an arbitrary device adopted for the sake of clarification. There is no rigid boundary between these categories, and both exhibit common features, such as a tendency toward inflexibility and repetition. This dual classification, however, also serves a theoretical purpose because of the assumption that the state of increased organismic excitability is the primary disturbance in fetishism, while the phenomena which chiefly represent attempts at control are secondary developments.

Such an assumption is related to concepts of earlier writers. Binet, in 1888, considered that the predisposition, present in fetishists, was that of a general nervous hyperaesthesia. Ellis (6) regarded fetishism as arising on a congenital basis, tending to occur in "... sensitive, nervous, timid, precocious individuals. ..." Raymond (30) has recently suggested that the predisposition proposed by Binet, represents essentially "an unusual capacity to form conditioned responses." This author accordingly employed aversion therapy, with apparent success, in one patient.

TEMPORAL LOBE DYSFUNCTION

Certain behavioral phenomena, in fetishists, which have been viewed as manifestations of an underlying increased excitable state seem analogous to known and hypothesized forms of temporal lobe dysfunction.

First, frank epileptic seizures, one clearly psychomotor, have been described in two cases. In both the fetish object was the stimulus for seizures.

Second, the "episodic symptoms," although not frankly epileptic, seem analogous in form and content to certain types of temporal lobe seizures. Reference is made to seizures which consist of one or combinations of the following: complex visual hallucinations (16, 29, 31), visual illusions (29), affective changes (7, 21, 29, 35), forced thought (5, 16) and complex motor acts. In these, the seizure material suddenly and involuntarily floods the field of consciousness. The material, usually repetitive, has a "screen" quality—with the latent content of psychodynamic significance (7). Analogues of other seizure types, such as those consisting of auditory hallucinations, have not been noted in the case material of fetishism.

Further, varied episodic symptoms, not conventionally epileptic, including those of a perceptual, affective and ideational nature, have also been described by Ervin, Epstein and King (8) in patients with temporal electroencephalographic abnormalities. Heath (13), employing deep electrodes, has demonstrated abnormal electroencephalographic activity in the septal region, rostral hippocampus and amygdala occurring simultaneously with episodic behavioral symptoms including among others, rage, forced verbalization (*e.g.* compulsive chanting of the Psalms), and hallucinations.

Third, the acute psychotic states of brief duration, reported in some fetishists, are of related interest in that similar types of psychoses have been noted in temporal lobe epilepsy (7, 26), in patients with temporal electroencephalographic abnormalities, who do not necessarily have clinical epilepsy (8, 15) and accompanying recording abnormalities in the septal region, rostral hippocampus and amygdala (13, 14). Monroe *et al.* (24, 25) have also suggested a link between epilepsy, acute psychotic states and other episodic symptoms.

The acute psychotic reactions reported in temporal lobe epileptics often have a content identical with that of the seizures. However, when the fetishist becomes acutely psychotic, the content of the psychosis seems singularly devoid of any direct reference to the fetish object itself, but instead consists of persecutory, hypochondriacal and grandiose material as well as visual hallucinations, forced motor activity and marked anxiety. This is perhaps another illustration

of the importance of the fetish as a means of maintaining control, of protecting against the release of potentially chaotic behavior. Indeed, in the case of one fetishist, an acute psychotic reaction was apparently precipitated by an attempt to abandon his fetish (28).

May the spontaneous involuntary appearance of the fetish object in consciousness also be related to temporal lobe seizure phenomena (forced thought or visual hallucination)? It will be recalled that in the case of Mitchell, Falconer and Hill, safety pin fetishism was the earliest symptom—as the years progressed, becoming incorporated but always remaining the initial manifestation of an unmistakable seizure. The fetish object itself, at least in this particular case, does, then, appear related to the epileptic process.

The occurrence of frank epileptic seizures in fetishists is too infrequent to justify formulating theoretical conclusions. However, if the "episodic symptoms" and acute psychotic states are also considered, and if one grants the existence of a relationship between these three, then the speculation may be permitted that a related underlying pathophysiologic mechanism in temporal lobe function is present in fetishists, which, in given patients, may be expressed in seemingly dissimilar forms: a conventional epileptic seizure, an acute psychosis, an episodic alteration in perception, affect, motility or ideation.

Unlike the episodic behavior, no ready analogy can be made between other manifestations of the increased state of excitability in fetishism, for example, markedly responsive orgastic behavior, and well-known types of human cerebral dysfunction. It is relevant, however, that among the behavioral abnormalities consistently noted by Kluver and Bucy (19) in bi-temporal lobectomized monkeys were hypersexuality and "an excessive tendency to take notice of and to attend and react to every visual stimulus." Sexual activity (copulation and self-stimulation) was increased; frequent erection of the penis occurred, often without previous manipulation. Should a monkey merely grab a finger of the observer, this "may be immediately followed by general bodily activity and penile erection." The monkeys seemed to be dominated by the tendency to contact every object as quickly as possible, including such items as "an eyelet in a board, a speck of dirt on a mirror, a scratch on the table, a nut in a motor, a stone in a ring, the foot of a toy monkey, a whiff of smoke, cuff buttons, a wrist watch and the mouth of the experimenter." A case of bilateral removal of the temporal lobes in man, reproducing the lack of inhibition and other features of Kluver and Bucy's syndrome, has been described (34).

RELATIONSHIP BETWEEN PSYCHODYNAMIC PATTERNS AND THE EXCITATORY STATE

Freud (9) considered castration anxiety the primary psychodynamic determinant in the genesis of fetishism and regarded the fetish object as representing a symbolic penis. Later writers have stressed the importance of aggression (27), of marked fear of separation from the mother (3, 36) and of impairment in the formation of the body image (12)— all factors operating in earliest life, anteceding but influencing later sexual conflicts. Payne (27) states that a determinant of fetishism is "the necessity to make a defense against an archaic sexual aim—the aim being to kill the love object."

All students of fetishism are struck by the marked condensation of meaning in the fetish object. Payne, in her case study, states that "every component of the infantile sexual instinct has some connection with the fetish object, so that this object is associated with all the repressed infantile sexual experiences." Wulff (37), drawing from observations by himself and others on the behavior of young children with fetish-like objects, comments that "in the young child, the fetish represents a substitute for the mother's body and in particular for the mother's breast." He stresses the importance of ol-

factory and tactile sensations in determining the choice of the object so that it will smell and feel like the mother's body.

There is general agreement that persistent identification with the mother, marked sexual fears, and powerful aggressive impulses are all prominent clinical features in the fetishist. However, not necessarily being unique for the fetishist, can they alone provide a full etiological explanation? These factors may gain more specificity if they are viewed as stemming from an underlying state of increased organismic excitability. From this standpoint, a psychodynamic formulation will be presented, tracing briefly the development of fetishism from its origins in early life onward. Much of this construction is hypothetical because of the difficulty in obtaining definite data, particularly in regard to the early mother-child relationship.

In infancy and early childhood, there is evidence of an unusually close physical relationship between the mother and child, as well as the suggestion that the maternal behavior is overly seductive (18). The intensity of the relationship is heightened by the uncommon impressionability and responsiveness of the child, assumed to be a correlate of the excitatory state. The maternal behavior, however, is also perceived as rejecting, producing desertion fears in the child, again of unusual intensity. The child's consuming need to possess the mother orally and manually, in the literal sense of both terms, is thwarted by the physical impossibility of such acts as well as by her rejecting behavior. The body of the mother cannot be completely possessed, but an object which has some associative link to the mother's body, can. This object is to become the fetish. At this stage, the fetish can be mouthed and fondled. It reduces motor tension and is of particular use during periods of increased desertion fear. The fetish is thus "engrammed" through an initial affectively charged perception of an object linked to the mother, and then by repetitive motor (oral and manual) activity.

As a repair for the fear of losing the mother, by her desertion of him or his oral destruction of her, and perhaps because of other factors, as yet unknown, the child forms an enduring sense of fusion with the mother. The primary identification never weakens. In time the fetish, which is originally equivalent to the mother's body, will, in fantasy and dream, be worn or otherwise joined to the fetishist's own body as a symbolic expression of the wish to completely possess, by being, the mother.

As development proceeds, stimuli from all the child's erogenous areas become linked to the fetish, which as a symbol of the earliest erotic strivings, has already assumed primacy in the psychic organization. During childhood, responsiveness to sexual stimuli is greater than that usually encountered. The earlier need to possess the mother orally, reinforces the current genital drives and heightens already intense sexual feelings. The immature sexual apparatus cannot discharge the sexual excitation, and anxiety may accompany the mounting tension. In this situation of increased excitation coupled with an unusually intense drive to possess (with its connotation of to destroy) the mother, castration fears are greatly magnified, and this, in turn, increases the anxiety. Again the solution is provided by the fetish, the symbolic mother that can be safely possessed. Drawing upon the earlier pattern, the tension is discharged on the fetish object. Another method of discharge is through sadistic behavior. The sadistic feelings themselves are unusually intense and, as has been noted in the fetishist, appear, along with other emotions, to be in a state of confluence with sexual feelings.

With the increase in sexual stirrings of adolescence and early adulthood, mutilation fears also gain in intensity. Possession by sexual intercourse is terrifying because it may annihilate both the fetishist and the woman. Therefore, the preoccupation with the fetish increases. Again, complete poss-s-

sion and the craving for fusion are obtained via the fetish object.

Not only the fetish object affords protection against the expression of tensions arising from the inner state of excitation. At both a conscious and automatic level, compulsive and obsessive mechanisms are also adopted. These defenses eventually are brought into use in a more and more automatic fashion so that any perception of undue tension is immediately countered by means of the fetish or some other obsessive thought or compulsive act. In effect, a dangerous impulse evokes a defensive maneuver so swiftly that the latter becomes indistinguishable from the former. Protection is also provided by retreat into fantasy; into the realm of thought and symbol rather than action. Masochistic fantasies are of particular value by serving the defensive need to submit and become a woman.

FURTHER THEORETICAL CONSIDERATIONS

As has been indicated, the fetish object remains indispensable throughout the fetishist's development. Although its symbolic significance becomes increasingly ramified with the years, the basic function (psychic adaptive value) of the fetish is always to reduce tension and provide control by serving as the object on which the intense sexual and aggressive drives, accompanying the need for maternal fusion, may be safely discharged.

Perhaps itself a product of disturbed cerebral function, the fetish, nevertheless, serves to control forces which threaten psychic disorganization. There is not sufficient data, however, to establish a definite relationship between loss of the fetish and precipitation of an acute psychotic reaction. Indeed, through psychotherapy, it is possible for the more integrated patient to gradually relinquish part of his dependence on the fetish without obvious ill effect. Perhaps the less bizarre the fetish object, that is, the closer it approximates a conventional symbol of the female, the less the prospect of a "psychotic" mental structure.

The mental structure of all fetishists, however, is characterized by the presence in consciousness, to a varying extent, of primary process material similar, for example, to that encountered in dreams. The fetish itself resembles a dream symbol; many of the episodic phenomena are similar in nature to manifest dream content. As another illustration, one may compare the orgastic behavior of the fetishist, awake, with that of normal erotic dreams in which psychic processes alone are the immediate stimulus for ejaculation.

The appearance of primary process material in consciousness during the waking state is generally regarded as indicating a failure in repressive mechanisms. In this study, such a failure in repressive mechanisms has been attributed to an increased excitatory state, which is assumed to be related, at least in part, to abnormal brain discharges. These discharges cause an eruption into consciousness of primary process material in the same fashion as such material appears during a temporal lobe seizure (7, 16). If the fetishist is an individual whose brain has, in some manner, been discharging abnormally since early life, cerebral inhibitory mechanisms may have been prevented from attaining full function, thus producing a disturbance in psychic integration. As a result, the perceptions of childhood as well as the emotional and thought processes of that era, are not assimilated and synthesized into the developing psyche, in the usual fashion, but instead retain their autonomy and their early intensity.

SUMMARY

Well-documented cases of fetishism in the literature and a case of the author's were studied in an attempt to gain a more comprehensive understanding of this disorder.

Certain characteristic behavioral phenomena encountered in fetishism are described. These phenomena can be divided into two general groups: the first representing a state of increased organismic excitability, the

second representing attempts to maintain organismic control.

The state of increased organismic excitability is considered the primary disturbance in fetishism. This state is regarded as a product of cerebral pathophysiology. Some of the major manifestations of this state appear to be related to seizure and other episodic phenomena found in temporal lobe dysfunction.

The psychodynamic patterns of the fetishist are discussed with particular reference to the role played in their formation by the state of increased organismic excitability; the adaptive value of the fetish object is also examined.

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PHENYLKETONURIA: A FURTHER STUDY

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In the 25 years that have elapsed since Folling first described phenylpyruvic oligophrenia (phenylketonuria) a moderate amount of research has been published. Our knowledge of the disease, its incidence, clinical description and related scientific data has increased immeasurably. With increased knowledge has also come some suggested treatment and the hope of prevention or early cure (8, 9, 17). There is no need for an extensive review of this work here since they are available elsewhere (12, 16, 17). Some of the major findings have been the pronounced degree of mental defect, the fair appearance of the great majority of cases, the specific biochemical and metabolic abnormalities, the high incidence of neuromuscular abnormalities, and the evidence pointing to a genetic disorder. The incidence in this country is judged to be about four per hundred thousand of the population at large.

Biochemically, phenylketonuria is characterized by the excretion of phenylpyruvic acid in the urine along with phenyllactic acid and phenylacetic acid. The high concentration of blood phenylalanine is probably the result of a decrease in activity or concentration of the enzyme, phenylalanine hydroxylase, which is required for the normal conversion of phenylalanine to tyrosine. This explanation has been substantiated by Jervis (11), who succeeded in converting phenylalanine to tyrosine by an extract of liver from normal persons, whereas a liver extract from phenylketonuric patients prepared in the same way, was unable to bring about this conversion.

Although the major features of this disorder have in general been confirmed, some of the findings reported in earlier studies have not always been validated in precisely the same degree (13, 17). Because of this it seemed worthwhile to report the findings on a study of 21 cases surveyed recently. Where possible an attempt will be made to relate our results to those reported in the literature and particularly to the recent study of 21 cases published by Wright and Tarjan (17).

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THE PRESENT STUDY

The present report is a study of 21 patients with phenylketonuria who were diagnosed at the Beatrice State Home in Nebraska by the $FeCl_3$ method (6). Subsequent quantitative determinations using 2,4-dinitrophenylhydrazine (15) confirmed the original test. Eleven of the 21 were females. Only one of the cases was originally diagnosed as a case of phenylketonuria. The remainder were institutionalized as mentally defective with varying diagnoses. An original survey of the 2000 resident patients in 1956 disclosed 15 cases. More recently another survey of patients admitted since that time revealed six additional cases.

RESULTS

Some of the basic information and findings on these cases are presented in Table 1. In general, these data are in accord with those reported in previous studies. All of the cases in the present group are Caucasians, who appear to account for almost all of the reported cases of phenylketonuria. Seventeen of these individuals had blue eyes, two are described as having hazel eyes, with only two having brown eyes. Fourteen were judged to have blonde or light brown hair. The remainder were considered to have brown hair, with only one having black hair. While our group is relatively small, the frequency of blue eyes is approximately 80 per cent which is slightly below the "over 90 per

TABLE 1

Summary Data On 21 Cases Of Phenylketonuria

No.	Sex	Eyes	Hair	Mental Status	IQ	Speech	Age at Adm.	Diagnosis At Adm.
1	F	Blue	Blonde	Idiot		Few words	3 yrs. 9 mos.	Familial
2	F	Blue	Lt. Brown	Idiot		None	4 yrs. 3 mos.	Epilepsy
3	F	Blue	Blonde	Idiot		Few words	15 yrs. 3 mos.	Undifferentiated
4	F	Blue	Lt. Brown	Imbecile	34	None	3 yrs. 3 mos.	Congenital
5	F	Blue	Blonde	Imbecile	18	Some	51 yrs. 7 mos.	Familial
6	M	Blue	Blonde	Idiot		None	16 yrs. 7 mos.	Familial
7	F	Blue	Blonde	Idiot	18	Few words	10 yrs. 2 mos.	Familial
8	M	Blue	Lt. Brown	Idiot		None	6 yrs. 4 mos.	Epilepsy
9	F	Blue	Blonde	Idiot	20	None	11 yrs. 4 mos.	Undifferentiated
10	M	Blue	Blonde	Idiot	25	None	2 yrs. 10 mos.	Phenylketonuria
11	F	Hazel	Blonde	Idiot		None	10 yrs. 7 mos.	Cerebral agenesis and M R
12	M	Hazel	Brown	Idiot	*20	Few words	12 yrs. 10 mos.	Cerebral agenesis and M R
13	F	Blue	Blonde	Imbecile	37	Some	13 yrs. 4 mos.	Familial
14	M	Brown	Brown	Imbecile	*20	Some	28 yrs.	Undifferentiated
15	M	Blue	Blonde	Severe Ret.	*25	None	7 yrs. 5 mos.	Trauma during birth
16	F	Blue	Lt. Brown	Severe Ret.	*20	None	11 yrs. 6 mos.	Cerebral maldevelopment with cerebral palsy
17	M	Blue	Brown	Severe Ret.	*20	None	14 yrs.	Trauma during birth —congenital
18	M	Blue	Brown	Severe Ret.	20–25	None	50 yrs. 3 mos.	Congenital cerebral maldevelopment with phenylketonuria
19	M	Blue	Brown	Severe Ret.	*25	None	57 yrs. 11 mos.	Congenital cerebral maldevelopment with phenylketonuria
20	M	Blue	Brown	Severe Ret.	*20	None	64 yrs. 9 mos.	Congenital cerebral maldevelopment with phenylketonuria
21	F	Brown	Black	Idiot		None	11 yrs. 10 mos.	Undifferentiated

* These are estimated IQ's indicating individual does not reach or exceed scores listed.

cent" mentioned by Jervis (12), but is more than the 13 out of 21 reported by Wright and Tarjan (17). With regard to color of hair, our findings are similar to those reported by Wright and Tarjan. Only 10 cases were judged to have blonde hair, although an additional four were deemed to have light brown hair. Some of the discrepancies may be due to the procedures for judging and categorizing hair color. Thus while most of these patients are characterized by blue eyes, fair skin, and blonde or light colored hair, not all of them have these physical features.

These results are not unexpected when the metabolism of phenylalanine is considered. Pigment production depends upon tyrosine which in turn arises normally through the metabolism of phenylalanine. However, tyrosine can be ingested directly in the diet and thus lead to melanin production independent of phenylalanine. On the other hand, high phenylalanine levels might inhibit tyrosine metabolism (5) and thus reduce pigment formation. One, therefore, might expect some variability concerning the frequency of blonde hair and blue eyes in this disorder.

Different types of data are available concerning the level of mental ability for these individuals. In only thirteen cases have psychological examinations been given. In sev-

eral instances these were either not attempted because of the obviously severe retardation or because the subjects were conconsidered essentially untestable. In those cases where IQ's were reported only two exceeded 25. In the remainder, a number are estimated at below 20 or 25 IQ because of obvious difficulty in securing a precise estimate of intellectual level. Five cases are classified as imbeciles with the remaining 16 categorized as idiots or severely retarded. The degree of mental retardation is thus severe and in general is in agreement with previous reports (2, 12, 14, 16, 17). Over 75 per cent would be classified as idiots with the remainder as imbeciles. However, five cases with IQ's above 70 have been reported in the literature (12, 14).

One of the findings in phenylketonuria which impresses most observers is the individual's lack of speech and inability to communicate verbally. In a survey of 106 cases, Paine (14) found that only about eight per cent do speak and that their speech is usually limited to single words. In two-thirds of the present cases there was no apparent speech, and in all but three of the remaining cases speech was limited to only a few words. One of the cases was able to converse in German about questions concerning herself and the institution. In most cases, however, there was no reply to questions asked by the examiner.

The behavioral patterns noted in these patients appear to vary considerably. Whereas Penrose (16) stated most patients with phenylketonuria were "good-tempered," Benda (2) described them as being aggressive and rather "wild" in behavior. The behavior of the individual apparently is related in part to the level of intelligence. Two of the individuals in the present study not only were pleasant and cooperative, but were able to perform a regularly assigned task in the institution. Only one was classified as destructive, although six others were frequently irritable, "nervous," or given to emotional outbursts or tantrums. In the latter group the individuals are much more prone to scratch or injure themselves than they are to assault or harm others. Several of them are very quiet, prefer to be by themselves, and are fearful of strangers or a change in environment. There does not appear to be any specific type of behavioral pattern which is associated exclusively with phenylketonuria or is descriptive of it.

As noted in Table 1, most patients were diagnosed as something other than phenylketonuria at the time of admission. In three recent cases, the presence of phenylketonuria was diagnosed shortly after admission when studies of this type were made. In only one instance was the diagnosis of phenylketonuria made prior to admission to the State Home. Apparently, relatively few tests for phenylketonuria are performed by medical practitioners or institutions in this geographical area.

Another point to be noted is the variation in age at which the individuals in our group were institutionalized. The age at admission ranged from two years, ten months to over 64 years. Four of the cases were under five years of age at admission while a similar number were 50 years or older. The reasons for admission and the particular time of admission appear related both to variables in the home situation and to those related to the individual's behavior and personality functioning. In most instances a decision is made that the individual no longer can be cared for at home. As is true with other types of mental deficiency, such decisions vary with the individuals and the circumstances involved. In five cases, the patient was institutionalized because of the advanced age of the mother. In this connection, it is interesting that three of the cases (Nos. 18, 19, 20) were brothers ranging in age from 50 to 64 years. These patients were recently admitted to the State Home because their mother was no longer able to care for them! All three of these brothers are severely retarded, two of them never walking and being largely confined to bed. The third brother was reported

to have helped his mother take care of the other two.

Phenylketonuria is considered to have a genetic basis with a simple recessive mode of inheritance (7, 10, 12, 16). In view of this, siblings of known phenylketonuric patients should be examined for phenylpyruvic acid in urine. A negative test before the 34th day after birth does not rule out the disease (1). Apparently a phenylketonuric infant does not excrete phenylpyruvic acid until after this period.

Because of the genetic aspect, it is of interest to elaborate somewhat more on the family mentioned previously which produced three cases of this disorder. In addition to the three brothers with phenylketonuria, there were five other siblings, all of them males. Three of them were apparently normal, married, and raised families. Two of these three are known to have had a high school education. No reference is made to problems pertaining to their children, although no systematic investigations have been made. A fourth brother, unmarried, was active socially in the community in which he lived, but later committed suicide. The fifth brother, also unmarried, was committed to a state hospital and died there after 22 years. In this family of eight siblings, three were thus diagnosed as cases of phenylketonuria, two others appeared to have significant personality disturbance, while the remaining three apparently led normal lives.

TREATMENT

In recent years a treatment for phenylketonuria based on a diet low in phenylalanine has been recommended. The diet consists of a protein hydrolyzate, from which the phenylalanine and some other amino acids have been removed. The hydrolyzate is then supplemented with a synthetic amino acid mixture lacking phenylalanine. Vitamins, minerals, and carbohydrates are also added.

A number of recent studies have reported the effects of such diets on children with phenylketonuria. While the results appear to be encouraging, as far as intellectual status is concerned they are still far from conclusive. Most of these studies report an increase in alertness, positive behavioral change, and increase in mental performance, although some negative findings have also been reported (3, 9). It should be stressed that while some changes in IQ appear to be statistically significant, the individuals may still function at a retarded level. For example, in a study by Clader (4), one case improved in IQ from 35 to 61 over a period of eleven months, while a second case improved from an IQ of 37 to 56 within a period of thirteen months. These appear to be significant changes, but both individuals are still functioning at retarded levels. It is obvious that longitudinal studies are needed to see if these changes continue to occur in a positive direction and what the limits of improvement might be. Thus far there have been no real long-term longitudinal studies. In the case of one infant examined initially at two and a half months of age and receiving the diet until the age of 20 months, approximately average results have been secured at both initial and later intellectual appraisals (9). On the other hand, Blainey and Gulliford (3), in a study of six cases given phenylalanine-restricted diets, did not obtain any marked improvement with their cases. Some of the subjects in the present study between 10 and 20 years of age were given these diets at our Institute. No clinical improvement was noted although phenylpyruvic acid excretion was lowered by the diet. For example, random samples averaging about 1.5 mg. phenylpyruvic acid/cc. of urine were decreased to .25–.30 mg./cc. Additional studies performed at a later date on early morning samples showed decreases from approximately 2.4 mg. phenylpyruvic acid/mg. of creatinine to essentially trace amounts.

SUMMARY AND CONCLUSIONS

A study of 21 cases of phenylketonuria was reported and comparisons made with

previous findings in the literature. While there were some slight deviations, in general, the present results are in agreement with those reported previously. Most of the patients are severely retarded, only a few can communicate verbally, and there is no one personality or behavioral pattern which can be said to characterize the group. Clearly there is a need for a state or nation-wide system of early diagnosis and screening to locate cases with phenylketonuria as soon as possible. While low phenylalanine diets appear promising as a means of treatment for cases discovered relatively shortly after birth, more research is needed to evaluate the long-term effectiveness of such treatment.

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URINARY AROMATIC METABOLITES IN SCHIZOPHRENIA

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INTRODUCTION

Studies of urinary aromatic substances have received psychiatric attention in recent years because 1) certain psychotomimetic agents such as LSD-25, bufotenin, and adrenochrome are characterized by the aromatic indole nucleus; 2) serotonin, a biologically active indole found in the central nervous system, has an unknown brain function; 3) two diseases exhibiting the symptom of mental deficiency, phenylketonuria (3, 37) and Hartnup's disease (27), are characterized by aberrant phenylalanine and tryptophane metabolism; and 4) the urine of schizophrenics has been reported to contain abnormal indoles (38, 49).

The evidence for increased excretion of aromatic metabolites in the urine of schizophrenics has recently been reviewed by McGeer *et al.* (32). However, there are few comprehensive studies of the excretion patterns of these metabolites.

This investigation was designed to survey the aromatic metabolites in the urine of schizophrenics by paper chromatographic techniques in order to assess the nature of the aromaturia.

METHODS

Urines were collected from 53 non-hospitalized, non-psychotic control subjects and 50 acute schizophrenic males and females.[2] Not more than two months had passed since the onset of psychotic symptoms in all patients and the majority had been hospitalized less than four days. A few had had previous psychotic episodes. Nearly all were very disturbed and 21 of these were under phenothiazine medication. The age range of these patients was from 16 to 64 years with a mean of 34 years. There were 27 females and 23 males. The controls comprised 50 males and three females ranging in age from 21 to 52 years with a mean age of 32 years. No dietary restrictions were placed on the subjects.

Overnight urine specimens were collected without preservative and usually processed the same morning of collection. Creatinine determinations were done according to the method of Folin (24). The creatinine concentration of each individual sample determined the volume of urine to be processed. If the concentration was greater than 2 mgm./cc., then 50 cc. of urine was used and diluted to a volume of 100 cc.; if less than 2 mgm./cc., 100 cc. of urine was processed.

Urines were processed according to Dalgliesh's method (15) because preliminary chromatographic trials comparing the ethyl acetate extraction method of Armstrong *et al.* (5) and the deactivated charcoal absorption method of Asatoor and Dalgliesh (6) had indicated that the latter yielded considerably more material positive to both diazotized sulfanilic acid and Ehrlich's reagent.

The urine sample was adjusted to pH 4 with glacial acetic acid (pH paper). To this was added 3 gm. of deactivated charcoal (8 per cent octadecylamine on N.F. activated charcoal) and stirred magnetically for at least 15 minutes. The mixture was filtered by suction and the charcoal with adsorbed material was washed with 75 cc. of distilled

[1] Department of Psychiatry, University of Washington School of Medicine, Seattle, Washington. This investigation was supported in part by a Research Grant, No. M-2552-CM, from the National Institute of Mental Health, Public Health Service; and by the State of Washington Initiative 171 Funds for Research in Biology and Medicine.

[2] Patients' samples were obtained through the cooperation of the staff of the Veterans Administration Hospital and King County Hospital in Seattle, Washington.

water. Elution of metabolites was accomplished with 50 cc. of aqueous phenol (8.1 per cent) and the charcoal further washed with 35 cc. of water. The aqueous phenol was removed under reduced pressure at 50° C. The phenol was completely removed by re-evaporation of added water (2x). A partial purification was accomplished by taking up the dried residue in isopropanol:methanol (1:1) and the mixture was centrifuged. After centrifugation, the extract was reduced to dryness in an air stream and a volume of the organic solvent was added such that 1 cc. contained the equivalent of 50 mgm. of creatinine.

PAPER CHROMATOGRAPHY

The equivalent of 5 mg. of creatinine of each extract (100λ) was spotted on two 14″ x 14″ Whatman No. 1 chromatographic papers each to be run in two different bidimensional systems. For quantitation purposes, the size of the spot was kept constant at 7 mm.

After trials of various solvent systems, the following were chosen:

A. For substances positive to diazotized sulfanilic acid (DZSA), the ascending system of Armstrong *et al.* (5) was chosen. This bidimensional system utilizes isopropanol-ammonium hydroxide-water (modified to 8:2:1) in the first direction and benzene-propionic acid-water (100:70:5) in the second. An hour equilibration was obligatory in the second solvent for good resolution. After drying overnight in a ventilated hood the paper was sprayed with DZSA.[3]

B. For substances positive to Ehrlich's reagent. To avoid degradation of many relevant indolic substances (15, 28) alkaline solvents were not used. The method of Dalgliesh (15) was chosen to resolve Ehrlich positive substances. This descending system used the organic layer of freshly prepared butanol-acetic acid-water (4:1:5) in the first dimension (5 hour equilibration) and 20 per cent potassium chloride in the second direction. After drying (4–5 hrs.), the paper was sprayed the same day with freshly prepared Ehrlich's reagent (14), [p-dimethylaminobenzaldehyde (2 per cent) in dilute hydrochloric acid (1:6)]. The fleeting and variable nature of the colored compounds formed with Ehrlich's reagent made it mandatory that a close observation be kept on the papers for at least one-half hour.

QUANTITATION OF SPOTS

Relative estimations of materials present in spots were done in the following manner:

The outline of each DZSA and Ehrlich positive spot was traced on paper. The spot was cut out and weighed to give an estimation of the surface area. The weight variation on equally sized spots was found to have a standard deviation of 2.2 per cent of the mean. The concentrations of materials on paper chromatograms have been indicated to be linearly related to the logarithm of the spot size (8, 21). However, repeated chromatographic trials in this laboratory of an urine extract at four different concentrations in the Armstrong system have shown that there is a direct relationship between the surface area of the spot and its concentration. The correlation coefficients (r) of the surface areas of 9 individual spots measured through 4 concentrations ranged from .793 to .919 (mean .883). (r at the one per cent level is .436, df = 33.) The slopes of these regression lines were variable. The distributions of mean surface areas for the nine spots under each concentration were intercorrelated. Six correlation coefficients

[3] 1) Sulfanilic acid 9 gm., hydrochloric acid 90 cc., q.s. 1 liter water. 2) Sodium nitrite (4½ per cent). 3) Sodium carbonate (20 per cent). Add equal volumes of 1 and 2; let stand in an ice bath for 5 minutes. Add 2 volumes of 3, mix, and spray immediately.

ranging from .951 to .996 with a mean r of .985 were obtained. With 7 df, a correlation must be .798 to be significant at the one per cent level. These findings indicate a highly significant linear and direct relationship between spot area and concentration across all four concentrations studied. The standard errors of the estimate ($\sigma y.x$) ranged from 5.2 per cent to 16 per cent of the mean.

To test the reliability of the rating system outlined above, small amounts (20 γgm.) of standard materials were spotted along with 10 urine extracts in the two different systems. The results indicated that the reproducibility of the ratings is such that the standard deviations are 11 per cent of the mean in both the DZSA positive and the Ehrlich positive concentration ratings. The sum of the weights of spot tracings in a chromatogram has been called its total concentration rating.

IDENTIFICATION OF SPOTS

Tentative identifications of spots on the chromatograms were based on the following:

1. Comparison of characteristics (Rf rates, color, and U.V. sensitivity) of known available compounds with urinary constituents in the chromatographic systems.
2. Comparative data from the works of Acheson *et al.* (1), Armstrong *et al.* (5), and Dalgliesh (15) using similar systems.

New symbols for spots were assigned as they appeared if distinct in Rf rates and color. For the DZSA positive spots, numbers 1 to 39 correspond to the same spot designations of Armstrong *et al.* (5).

RESULTS

NUMBER OF METABOLITES

The urines of both schizophrenic and control subjects contained a total of 71 different spots in the Armstrong system and a total of 76 spots in the Dalgliesh system, of which the great majority are not identified. There is a probable duplication of many of these substances because of the sensitivity of some metabolites to both spray reagents.

TABLE 1

Metabolites Which Occur Only in Either Control or Patient Group

System	Number of Metabolites		Occurrence
	Controls Only	Schizophrenics Only	
Armstrong	10		5 or less chromatograms
Armstrong		12	2 or less chromatograms
Dalgliesh	13		2 or less chromatograms
Dalgliesh		23	5 or less chromatograms

In the Armstrong system a total of 59 metabolites has been found in controls, and in the schizophrenics, 61 metabolites; of these, 49 metabolites are common to both. In the Dalgliesh system the control group has a total of 53 metabolites and the schizophrenics, 63 metabolites, with 40 metabolites common to both groups. Thus, in both systems there are some metabolites which are present in one group but not in another. Table 1 shows the number and occurrence of these metabolites.

In the Armstrong system, 10 metabolites which were present only in the control group occurred in five or less chromatograms. In the same way, 13 Dalgliesh metabolites were present only in the control group, but they occurred in only one or two chromatograms. Unusual metabolites also were present in the schizophrenic group in both systems. The infrequency of these metabolites would indicate that they are probably of unusual dietary origin. No compound was found which regularly characterized the urine of schizophrenics.

Comparative results between the schizophrenics and control subjects are shown in Tables 2 and 3 which also give the designations, probable identity, characteristics, and relative frequencies of some spots found

TABLE 2

Characteristics of Some Spots[a] Found in Armstrong System with DZSA and Their Comparative Excretions in Controls and Schizophrenics

Spot Designation	Tentative Identification	Color	Mean Rf Rates[b]		Controls (Mean weight in mg. of spot tracing)		Schizophrenics (Mean weight in mg. of spot tracing)		t	% Relative Frequency[e]
			Isopropanol-Ammonia[c]	Benzene-Propionic Acid[d]	Mean Concentration Ratings	S.E.M.	Mean Concentration Ratings	S.E.M.		
1	p-hydroxyphenylacetic acid	Purple	0.36	0.42	36.0	1.87	41.6	2.07	2.007*	99
10	3 methoxy-4-hydroxy-mandelic acid	Light red	0.29	0.12	0.821	0.400	3.02	0.749	2.591*	13
17	Vanilloyl-glycine	Orange pink	0.19	0.13	7.10	0.600	4.20	0.610	3.388**	88
24		Yellow	0.30	0.38	15.5	1.74	8.29	1.76	2.907**	64
A		Orange	0.29	0.50	32.6	2.90	24.6	2.16	2.210*	91
D		Red pink	0.25	0.0	16.3	1.55	8.35	1.61	3.565**	70
J		Light orange	0.19	0.17	6.05	0.680	10.6	1.00	3.760**	63
UU		Purple	0.36	0.10	0.764	0.300	3.11	0.770	2.845**	11
Mean total concentration ratings					491.8	17.4	490.7	15.0	0.048	
Mean no. of spots					21.2	0.450	20.5	0.431	1.124	

[a] Only spots found to be significantly different.
[b] Mean of 20 determinations or less.
[c] S.D. ± 7.1%.
[d] S.D. ± 8.5%.
[e] As found in 76 control subjects.
* Significant at 5% level (1.984).
** Significant at 1% level (2.626).

in the Armstrong and Dalgliesh systems, respectively. For the sake of brevity, only those spots found to be significantly different in excretion are listed.

As shown in Tables 2 and 3, the mean number of metabolites present in the chromatograms of controls and schizophrenics in both systems is not significantly different.

TOTAL CONCENTRATION RATINGS OF METABOLITES

The mean total concentration ratings of metabolites in the chromatograms of schizophrenics and controls in both systems are shown in Tables 2 and 3. While in the Armstrong system there is no significant difference between these two groups in the total amounts of metabolites sensitive to DZSA, in the Dalgliesh system there is a significant difference in the amounts of Ehrlich reagent positive materials.

INDIVIDUAL METABOLITES

Table 3 shows that the Ehrlich reagent-positive metabolites that are found in increased amounts in schizophrenics' urines are compounds 1, 4, 5, 6, 18, 29, 48, and 51. Of these eight, four are tentatively identified as follows:

Spot 1	Indican
Spot 4	5-Hydroxyindoleacetic acid
Spot 5	Indoleacetic acid
Spot 6	Urea

TABLE 3

Characteristics of Some Spots[a] Found in Dalgliesh System With Ehrlich's Reagent and Their Comparative Excretions in Controls and Schizophrenics

Spot Designation	Tentative Identification	Color	Mean Rf Rates[b]		Controls		Schizophrenics		t	% Relative Frequency[e]
			Butanol-Acetic Acid[c]	20% Potassium Chloride[d]	(Mean weight in mg. of spot tracing)					
					Mean Concentration Ratings	S.E.M.	Mean Concentration Ratings	S.E.M.		
1	Indican	Tan	0.59	0.65	52.2	2.97	61.8	3.21	2.197*	99
4	5-hydroxyindoleacetic acid	Blue	0.78	0.44	45.6	2.43	56.9	2.34	3.343**	100
5	Indoleacetic acid	Violet → fades	0.87	0.48	23.0	2.51	36.1	4.33	2.620*	80
6	Urea	Yellow	0.69	0.87	50.2	1.93	59.8	2.03	3.429**	99
17		Violet → fades	0.73	0.80	14.3	2.19	7.06	1.79	2.558*	50
18		Yellow	0.85	0.81	28.8	2.40	38.8	2.77	2.732**	88
29		Light orange	0.84	0.52	17.1	3.01	28.9	4.47	2.189*	32
30		Green (late)	0.97	0.09	5.38	0.602	2.65	0.741	2.856**	54
48		Violet	0.85	0.88	8.29	1.71	19.7	2.46	3.813**	50
51		Yellow	0.51	0.83	0.528	0.380	4.30	1.18	3.040**	8
Mean total concentration ratings					519.4	16.6	623.0	16.1	4.437**	
Mean no. of spots					15.9	0.363	15.5	0.480	0.498	

[a] Only spots found to be significantly different.
[b] Mean of 20 determinations or less.
[c] S.D. ± 5.5%.
[d] S.D. ± 3.4%.
[e] As found in 76 control subjects.
* Significant at 5% level (1.984).
** Significant at 1% level (2.626).

Although there is no significant difference in total amounts of diazo-positive materials between schizophrenics and controls in the Armstrong system (Table 2), there is a difference in the excretion of individual metabolites. Three metabolites are found in greater quantities in schizophrenics, compounds 1, 10, J, and UU, but there is a lower excretion of metabolites 17, 24 A, and D. Compounds 1, 10, and 17 are tentatively identified as p-hydroxyphenylacetic acid, 3-methoxy, 4-hydroxymandelic acid, and vanilloylglycine, respectively.

DISCUSSION

The present findings indicate that there is an increased excretion of aromatic metabolites in the urines of schizophrenics. This alteration is not in the increased excretion of phenolic acids but in the increased excretion of indolic substances, contrary to the findings of McGeer *et al.* (33). The increased aromaturia is primarily quantitative for no metabolite has been found to be regularly excreted by schizophrenics which is not excreted by control subjects. The metabolites that were found only in the urines of one group or the other occurred too infrequently to evaluate their significance.

The absence of qualitative differences in this study is contrary to the report of Feldstein *et al.* (19) who found qualitative and quantitative difference in the indolic excretions of schizophrenics while Riegelhaupt

(38) and Sherwood (49) have reported the findings of different abnormal indoles in the urines of schizophrenics. Other investigators have not found Sherwood's unusual metabolite (18, 30, 33, 42), but Feldstein *et al.* (19) have confirmed the increased frequency of appearance of Riegelhaupt's quickly fading blue spot. The inability of this study to show qualitative differences may be due to differences in the method used or to differences in the schizophrenic samples.

The present findings of larger amounts of urinary 5-hydroxyindoleacetic acid (5-HIAA) in acute schizophrenics implying increased endogenous production of serotonin (52) is important in view of the present interest in the role of this amine in the central nervous system. The evidence which relates serotonin to brain function has been recently reviewed by Page (36). Investigators have not agreed on the comparative excretion levels of urinary 5-HIAA in schizophrenics. Some have found it increased (7, 42); some have found no difference from controls (20, 23, 39, 47); while Leyton (30) reported a decreased excretion.

The increased excretion of indoleacetic acid (IAA) in acute schizophrenics found in these studies is of considerable interest in view of its increased excretion in a variety of disease states (49), including two conditions characterized by mental deficiency, phenylketonuria (3, 26, 49) and Hartnup's disease (27). It is further intriguing that two of its precursors, tryptamine (18) and dimethyltryptamine (51) have been shown to have psychotomimetic properties.

Ross (44) and Sherwood (49) reported the findings of increased excretion of IAA by schizophrenics while others (7, 19, 30, 42, 53) have not found an excessive excretion. Indoleacetic acid, a normal urinary constituent, is not a product of bacterial action in the gut (43). It may be derived from two possible pathways in the metabolism of tryptophane (53), via tryptamine or via indolepyruvic acid. The weight of evidence favors the tryptamine route since tryptamine is normally found in urine (41) and injected tryptamine is degraded by monamine oxidase to IAA (16, 17, 50).

As in the present studies, Marquat (35) and Sano (46) found increased amounts of indican in the urine of schizophrenics; Borden (11) and Riegelhaupt (38) did not. It is generally accepted that indican is the urinary excretory form of indole formed from tryptophane by intestinal flora since treatment with antibiotics has led to a reduction or elimination of urinary indican (27, 34). There is evidence, however, that the source of indican may not be completely due to gut bacterial action (40).

The finding in this study of increased urea excretion in these schizophrenics may be related to their emotional disturbance. This may arise from increased overall protein catabolism as a consequence of the known activation of the pituitary-adrenal axis in emotional stress (9).

Most authorities (2, 12, 25, 31) report normal blood and urinary urea values in schizophrenia. However, Rowntree and Kay (45) in their longitudinal studies of schizophrenics through active and remission periods found that there was an inverse relationship between their blood urea and urinary urea levels and that during acute exacerbations there were changes in urinary urea levels. Gjessing (22) studied variations in nitrogen balance in "endogenous psychoses" in studies over a period of time and found that these variations were due to changes in the excretion of urea with increased nitrogen excretion occurring during "unrest" and that this occurred prior to the actual physical unrest.

The findings of increased amounts of indoleacetic acid, 5-hydroxyindoleacetic acid, indican, and urea have been discussed individually. Since all but urea are metabolites of tryptophane, this suggests an altered tryptophane metabolism in schizophrenia.

Speculation on the role of disturbed tryptophane metabolism in schizophrenics must be cautious since the exact fate of ingested

tryptophane is unknown. In contrast to control subjects, schizophrenic patients, even with tryptophane loading, did not show kynurenine, anthranilic acid, and 3-hydroxyanthranilic acid in urine while other tryptophane metabolites were found and increased after tryptophane (7). Zeller (54) reported abnormally high excretion levels of xanthurenic acid in schizophrenics and an inability to excrete higher levels of 5-HIAA after tryptophane loading. Kopin (29), however, found no difference between urinary excretion of 5-HIAA in schizophrenics and controls before or after tryptophane ingestion.

The above findings are to be regarded as tentative in view of the following uncontrolled variables. 1) While the majority of our patients (36 of 50) had been in the hospital less than four days, there is evidence that "institutionalized" patients show different indolic excretion patterns from non-institutionalized patients (4). 2) It is problematical whether differences in sex distribution between the patient and control population are the cause of these findings (30, 39). 3) Since chlorpromazine is said to reduce the excretion of 5-HIAA (13, 47), it is unlikely that the phenothiazine medication in 21 of our patients was the reason for increased indolic excretion. 4) The most pertinent variable bearing on the result is the diet since it has been shown that dietary factors may alter the urinary aromatic excretion pattern (48, 10), although it must be mentioned that coffee affects primarily the phenolic acids which were not significantly different in the two groups and that only five of the 50 patients had a banana in the diet.

This study suggests a defect in tryptophane metabolism in acute schizophrenia along routes which favor excretion of 5-HIAA, IAA, and indican. Whether these tryptophane metabolite differences are attributable to a specific disease process or associated with the non-specific biochemical accompaniments of emotional disturbance is not clear.

SUMMARY

The urinary excretion of aromatic metabolites of a group of 50 "acute" schizophrenics has been surveyed and compared with a group of 53 non-psychotic control subjects.

The increased aromaturia in schizophrenics was due to an increased excretion of indolic substances, not of phenolic acids.

No metabolite was found which regularly characterized the urines of schizophrenics.

Greater excretion levels of indoleacetic acid, 5-hydroxyindoleacetic acid, indican and urea were observed in the schizophrenic group.

The possible significance of these findings is discussed in terms of association with the disease process or the disturbed emotional state of the acutely ill patients.

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STUDIES ON THE URINARY EXCRETION OF 5-HYDROXYINDOLACETIC ACID AND 17-HYDROXYCORTICOSTEROIDS IN PATIENTS TREATED WITH MARSILID[1]

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Inhibitory effects of Marsilid on monoamine oxidase were demonstrated first *in vitro* (34). A similar drug action on this enzyme and the ensuing accumulation of substrates (serotonin and catecholamines) were shown also in animals (23, 29, 31, 35) and in humans (24). The urinary excretion of 5-hydroxyindolacetic acid, the end product of serotonin metabolism, did not decrease in Marsilid-treated men (11), as one might expect, but it was reduced when an excess of serotonin was produced in the human body by carcinoidosis (14) or various experimental procedures (8, 26, 32). Efforts were made to determine whether the effects of Marsilid or other monoamine oxidase inhibitors on the degradation of serotonin (17, 26, 32, 35) paralleled those on psychic functions and on blood pressure but the results were contradictory (8, 15, 16, 28). The findings were similar in analogous experiments on catecholamines (9, 20, 21) and tryptamine (28). Other investigations concerning metabolic effects of Marsilid in man include studies of drug action on blood sugar (33) and electrolytes (32). To our knowledge, adrenocortical reactions to Marsilid have not been studied in man, but, according to one paper (12), this endocrine function was profoundly affected by isoniazid, a compound which is chemically related to Marsilid and is believed to cause psychoses occasionally.

In this study we investigated the effects of Marsilid on the degradation of serotonin and on adrenocortical functions. The latter investigation was suggested by the fact that both Marsilid and cortisone show some similarity in their euphorant, appetite stimulating and anti-inflammatory actions (4, 22).

MATERIALS AND METHODS

The subjects selected for this investigation were three male patients (Cases I, II and III, aged 35, 60 and 46) and a female patient (Case IV, aged 26) from a ward for pulmonary tuberculosis, and a healthy male (Control, aged 46). All the patients had active tuberculosis but were afebrile and free of acute toxic manifestations at the time they were included in this project. In addition, they suffered from mental depression, anorexia and asthenia; the first patient also had a multitude of hypochondriacal and psychosomatic manifestations and the fourth patient reacted to emotional stress with gastric symptomatology. Marsilid was administered to the subjects for periods ranging from 20 to 27 days and was withdrawn when satisfactory clinical improvement or toxicity was observed. When symptoms of depression reappeared, treatment was reinstituted and continued for periods ranging from 11 to 39 days (Figure 1). The daily dosage was 100 mg. in two divided oral doses in all cases except the first patient who received 150 mg. of Marsilid during the first 12 days and 50 mg. during the balance of the first period of drug administration. The clinical evaluation of the patients' mental condition was based on two psychiatric

[1] Marsilid (iproniazid phosphate), manufactured by Hoffmann-La Roche, Inc.

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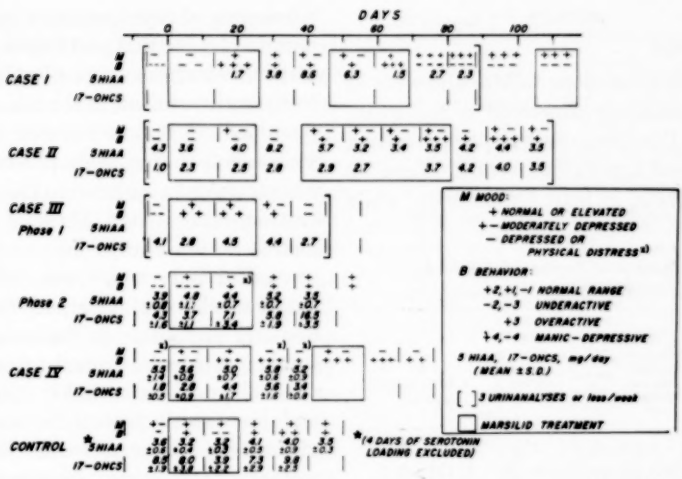

FIG. 1. Changes in mood and behavior: 24 hour urinary excretion of 5HIAA and 17-OHCS.

interviews a week and information obtained from the hospital personnel. The criteria used to rate the subjects' mood and behavior will be reported below.

Daily urinary excretion of 5-hydroxyindolacetic acid (5-HIAA), 17,21-dihydroxy-20-ketosteroids (17-OHCS), sodium, potassium, chloride, creatinine and in one subject total neutral 17-ketosteroids were measured. (In the preliminary stage of the investigation, which included studies on cases I, II, and III [during the first phase of treatment] urine samples were collected only two or three times a week, as indicated in Figure 1.) The authors whose methods were used were as follows: Udenfriend *et al.* for 5-HIAA (30); Reddy *et al.* for 17-OHCS (19); Berry *et al.* for Na and K (3); Cotlove *et al.* for Cl: (5); Peters for creatinine (18); Holtroff and Koch for 17-ketosteroids (13). Serotonin creatinine sulphate was administered by mouth daily to the control subject in six equally spaced doses of 4.0 mg. (equivalent to 1.85 mg. of serotonin) for three consecutive days during the base period, a procedure which was repeated twice during and twice after treatment. This load-test differed from the one devised by

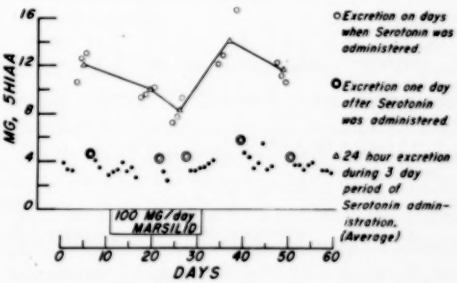

FIG. 2. Twenty-four hour urinary excretion of 5HIAA (control subject).

Sjoerdsma *et al.* (27) in that the latter authors used significantly larger doses of Marsilid (100 mg./8 h.) and serotonin (approximately 20 mg./8 h.). The data reported in Tables 1 and 2 and Figures 1–4 represent total excretion values in 24 hour urine specimens.[3]

[3] The findings were not evaluated on the basis of mean values of creatinine excretion because its metabolism seemed to be affected by Marsilid. Urinary creatinine which was 1.11 Gm./24 h. in the base period of the third patient rose to 1.29 Gm. during treatment and from 1.08 to 1.29 Gm. in the fourth patient. This increase might have been dietary. In the control subject, whose diet was better controlled, there was a reduction of urinary creatinine from 1.77 to 1.64 Gm. ($p < 0.001$) (Figure 4).

RESULTS

CLINICAL DATA

The psychic reactions to Marsilid were of the type commonly described in the treatment with this drug. Subjective well-being and improved appetite were experienced by all the subjects, at least temporarily, while a lessening of psychosomatic symptoms was reported by the first and fourth patient. The asthenic syndrome was also favorably affected by treatment, in that the capacity for sustained effort was restored to normal in all subjects during some phase of drug administration. In addition to this anti-depressant action on mood, Marsilid had a stimulatory or inhibitory effect on the patients' general activity which was reflected in behavioral changes. Overactivity was particularly noticeable in the emotionally less stable individuals. Thus the first patient, an alcoholic, exhibited frankly manic behavior and the fourth patient, a female with a moderately severe neurosis, became argumentative and overinvolved in a great number of tasks. On the other hand there was a decrease of activity in the third patient who complained of somnolence during the second course of treatment and in the control subject who experienced lassitude and muscular weakness during the second half of the period of drug administration. The output of energy was not substantially in-

TABLE 1

Significance of Increased 5-HIAA Excretion After Marsilid

	I Second period during Marsilid	II Comparable period after Marsilid	III First period during Marsilid	*P*
Case III Phase 2	4.4* ±0.23	5.2 ±0.22	4.8 ±0.31	I:II 0.02 I:III>0.3
Case IV	5.0 ±0.21	5.8 ±0.19	5.6 ±0.30	I:II 0.01 I:III>0.1
Control (4 days of serotonin loading excluded)	3.2 ±0.15	4.1 ±0.19	3.2 ±0.18	I:II <0.01 I:III 0.5

* Mean 5-HIAA(mg/day) ± S.E.

TABLE 2

Behavior and Activity Changes in Relation to the Excretion of 17-OHCS

	Maximum Activity†	Minimum Activity†	*P*	Comparable periods of activity		*P*
Case III‡ Phase 2				−− 4.3* ±0.49	−−− 3.7 ±0.31	0.3
Case IV	+++[a] 4.4 ±0.50	−−− 1.8 ±0.17	<0.001	+++ 4.4 ±0.50	+++ 5.6 ±0.51	>0.1
	+++[b] 5.6 ±0.51	−−− 1.8 ±0.17	<0.001			
Control	++ 9.8 ±0.83	−− 3.9 ±0.75	<0.001	+ 8.0 ±1.20	+ 7.3 ±0.91	0.7

* Mean 17-OHCS(mg/day) ± S.E.

† See Figure 1.

‡ Abnormally high 17-OHCS values during cardiac stress not used. (See Figure 3.)

[a] Second period of Marsilid.

[b] Period after Marsilid.

fluenced by these drug effects in any individual, because the patients had minimal ward privileges and the control subject did not change his daily routine during the experimental period. The first patient was an exception in that his state of overstimulation gave rise to increased motoric activity. Changes in mood did not parallel necessarily stimulating (or inhibiting) effects of Marsilid. For instance, the control subject was relaxed and alert despite wide fluctuations of his state of activity. Similarly the fourth patient became emotionally and physically distressed after treatment although she continued to be productive in occupational therapy for several weeks. Changes in mood were evaluated in terms of the patient's facial expression, body weight, capacity for sustained effort, and particularly of his subjective feelings. Behavior and activity were assessed on the basis of bed-side occupation, verbal productivity and interpersonal relationships. The anti-depressant and stimulating effects of Marsilid were rated and tabulated separately in an attempt to correlate them graphically with biochemical data (Figure 1). (The symbols used in this table to rate changes in mood were adequate but were less satisfactory as regards effects on activity and behavior.) The main physical manifestations were cardiovascular. The first patient developed orthostatic hypotension at the end of the first treatment period, the fourth patient at the end of the second. The second subject displayed some confusion and compulsive activity (in all likelihood of cerebro-vascular origin) a week before the termination of the second treatment period, and the third patient suffered from coronary occlusion and then from myocardial infarction (Figure 3). These data will be reported in greater detail elsewhere.[4]

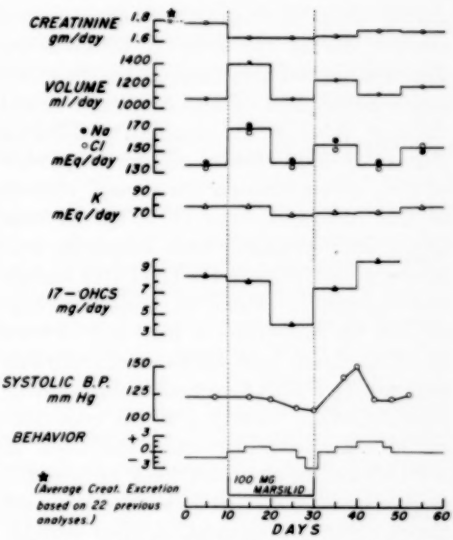

FIG. 4. Synopsis of chemical and clinical findings (control subject).

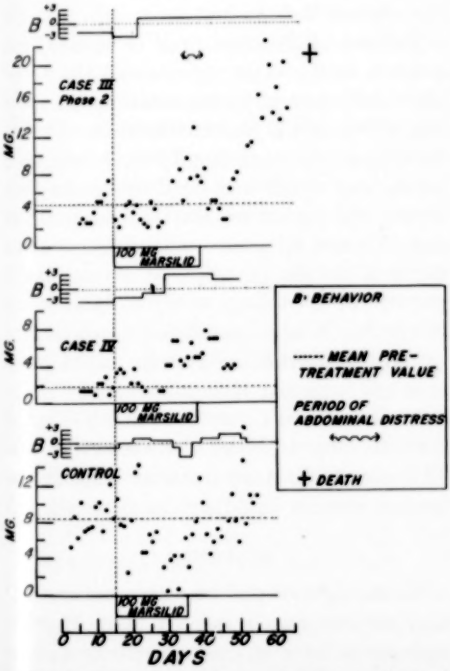

FIG. 3. Twenty-four hour urinary excretion of 17-OHCS.

BIOCHEMICAL DATA

5-Hydroxyindolacetic acid (*5-HIAA*) excretion did not follow a consistent pattern

[4] Angiology. In press.

during drug administration but increased sharply during the interval between the first and second treatment in the first two cases. Subsequent results confirmed initial findings. Whereas the excretion of 5-HIAA did not decline substantially in the process of drug administration the urinary content of this metabolite was 14 to 24 per cent higher after treatment than during the preceding period (Figure 1). The latter feature was significant (Table 1) and was exaggerated by the serotonin load-test (Figure 2). This figure also shows a considerable decrease of 5-HIAA excretion during drug administration, namely a 45 per cent deficit of exogeneous serotonin converted to 5-HIAA during the third week of Marsilid treatment as opposed to a four per cent deficit prior to treatment. A clear correlation between data on the excretion of 5-HIAA and psychophysical manifestations was not apparent.

17-Hydroxycorticosteroid (17-OHCS) excretion fluctuated considerably throughout the experiment. The scattering of data was substantially greater during and after the administration of Marsilid than during the base period (Figure 3). The levels of urinary corticosteroids were not related to the anti-depressant action of the drug but reflected variations in the patients' behavior and stress. This was not too apparent in Cases II or III (first phase) due to the shortcomings of the method used to rate behavioral changes and the limited number of urine samples tested for 17-OHCS. However, Figure 3 and Table 2 which were based on daily collections revealed the following facts. The output of 17-OHCS decreased in Case III during the first part of the second course of treatment during which period the patient complained of somnolence. This drug effect was not conspicuous clinically nor did the excretion of 17-OHCS vary significantly until cardiac complications developed. Then the urinary content of corticosteroids rose to a level which was four times higher than that of the pretreatment period. It is worth mentioning that the amount of 5-HIAA excreted during the same period was within base line values, a fact suggesting that the metabolism of serotonin was not affected by physical stress. (The patient did not exhibit any sign of emotional stress until he developed circulatory failure 24 hours before he expired.) The fourth patient suddenly became more energetic at the beginning of the third week of drug administration when the elimination of corticosteroids also began to increase abruptly. The control subject, on the other hand, became progressively more sluggish as the content of 17-OHCS in urine declined to pathologically low levels. The aforementioned fluctuations of adrenocortical activity might reflect variations in the expenditure of physical energy secondary to drug effects on behavior. This factor could not have been too significant, considering that the daily routine and physical activity were essentially the same in all the subjects but the first.

Sodium, Potassium and Chloride increased in the urine samples of the third and fourth patient during treatment, a finding which could be attributed to dietary factors. In the control subject, whose food intake and weight remained fairly constant during the period of Marsilid administration, Na and Cl varied with the output of fluids while the excretion of K was independent of the volume of urine. An increase of the Na/K ratio paralleled a decrease of urinary 17-OHCS, of systolic blood pressure and muscular strength.

17-Ketosteroids which were studied in the control subject varied between 10.7 and 13.2 mg./24 h. A clear trend in their excretion pattern could not be detected.

DISCUSSION

In the light of previous observations (6) and clinical data presented here, Marsilid appears to have at least two distinct pharmacologic effects: one is antidepressant and leads to a better psycho-physical integra-

tion, the other is stimulating (or inhibitory) and thus influences the individual's activity and behavior. The latter effect may become excessive and create a situation of stress and homeostatic imbalance. Due to the multitude of drug actions and numerous side-effects, which cannot be avoided even in optimal therapeutic situations, the metabolic alterations in Marsilid-treated patients must be exceedingly complex. Barsa (2) also attributed to the drug more than one psychopharmacologic action but he did not distinguish between its anti-depressant and stimulating effects.

Previous studies on the excretion of 5-HIAA in humans proved that subjects treated with amineoxidase inhibitors could not fully convert an excess of endogenous (14) or exogenous (27) serotonin into its final waste product but failed to indicate whether the metabolism of serotonin was reduced in ordinary therapeutic situations. In fact, Sjoerdsma *et al.* (26) doubted whether the small doses of Marsilid currently used in the treatment of depression had any effect on the metabolism of serotonin. Our findings on the excretion of 5-HIAA confirmed the data of Granowitz and Pletscher (11) (based on ten days of Marsilid administration) in that the anticipated decrease of 5-HIAA excretion failed to occur even after three weeks of drug administration. On the other hand the increase of urinary 5-HIAA observed after treatment provided indirect evidence that the metabolism of serotonin was affected by small but therapeutically effective doses of Marsilid. Furthermore 5-HIAA excretion was significantly reduced in our load-test which was less severe than that devised by Sjoerdsma's team (27) and was carried out with therapeutic dosage of the drug. This pharmacologic effect was not clearly related to psychic or other clinical reactions.

The output of 17-hydroxycorticosteroids was not uniform, an expected finding, considering that there was wide individual variation in response to Marsilid. The urinary content of 17-OHCS was not related to antidepressant effects but to changes in the patient's behavior and to internal stress. The latter effects were caused either by direct drug action on the pituitary-adrenal system or by an intermediate metabolic process with secondary involvement of the adrenals. Whatever the mechanism, this drug effect was sufficiently intense in one case to produce signs of adrenocortical insufficiency: increased Na/K ratio in urine, low levels of urinary corticosteroids, a drop in systolic blood pressure, and muscular fatigue. It should be mentioned here that Ayd (1) described lassitude and weakness in 39 per cent of Marsilid-treated individuals, a syndrome which might very well be related to adrenocortical insufficiency. Whether other drug effects are also mediated by the pituitary-suprarenal system awaits further studies. Sexual impotence, another common side-effect, which occurred in one subject, was not caused by drug action on the adrenals inasmuch as the excretion of 17-ketosteroids was essentially unchanged in this case. Marsilid-induced fatigue, which we attributed to adrenocortical imbalance, is a condition which necessitates early recognition and may require corrective measures.

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THE EXCRETION OF URINARY PHOSPHATE IN SCHIZOPHRENIA

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In the course of investigations of adrenocortical activity and response in schizophrenic and normal men it has been observed that the urinary excretion of inorganic phosphate is lower in the schizophrenic than in the normal man (3, 6). It has been suggested that the administration of adrenocorticotrophin causes an increase of this excretion in the schizophrenic (3), but when the spontaneous trend of the underlying diurnal variation was taken into account no net increase was observed (6). The following investigation was undertaken to determine if the lower excretion of phosphate by the schizophrenic patient applies to a whole twenty-four hour day or is only an apparent difference due to differences in diurnal cycle between schizophrenic and normal men.

PROCEDURE

The metabolic studies were conducted on the Clinical Investigation Ward. Apparently healthy hospital orderlies served as normal subjects. Elderly men, who were in good health for their age, and who were under domiciliary care at Westminster Hospital, volunteered to serve as elderly normal subjects. The chronic catatonic and paranoid schizophrenic men were obtained from the psychiatric service of Westminster Hospital.

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All the subjects were free from the physical diseases that are known to affect the metabolism or excretion of phosphorus. The number and the mean age with standard deviation and range of the various groups were:

	No.	Age Mean	Age Range
Normals	21	35 ± 7.4	21–47
Catatonics	23	38 ± 5.8	24–48
Paranoids	18	41 ± 6.8	24–51
Elderly-normals	14	74 ± 7.1	63–88

Urine was collected over 24 hours in five periods (7:30–11:30 a.m.; 11:30 a.m.–3:30 p.m.; 3:30–7:30 p.m.; 7:30–11:30 p.m.; 11:30 p.m.–7:30 a.m.). On each specimen the volume was measured and the inorganic phosphates determined. In one study total phosphorus was also determined by digesting the urine with perchloric acid before measurement of inorganic phosphate. A sample of venous blood was drawn at 11:30 a.m. and the serum inorganic phosphate determined by the method of King (4).

The patients were tested in both the fed and fasting states. In the first (fed) study the subjects went to the Clinical Investigation Ward following breakfast. They arrived in time to empty their bladders at 7:30 a.m. and so start the first collection period. During the next 24 hours on this ward they received the regular hospital meals with no restrictions on intake of either food or fluid.

For the second (fasting) study the subjects arrived at the ward following their evening meal, in time to start the first collection period at 7:30 p.m. There was no restriction on the intake of water but they were given only token meals so that the total intake was 163 Calories and 23 mg. of phosphorus. This investigation, the effect of near-starvation for 24 hours on the phosphate excretion of the schizophrenic subjects, was carried out to define more clearly the

difference in phosphate excretion between schizophrenics and normals.

If schizophrenic patients were on phenothiazine drugs they repeated both studies after two weeks without the drug; those who were not already receiving one of these drugs repeated the studies after two weeks of such therapy. It was regrettable but unavoidable that arrangements could not be made to obtain volunteers who would take these phenothiazine drugs for a period of investigation so that their effect on phosphate excretion in the normal could be determined.

RESULTS AND DISCUSSION

A preliminary analysis had shown a correlation between daily output of phosphate and individual deviations from the average body weight of the Canadian standard (5). Therefore only those subjects within ±10 per cent of the average weight for their height and age according to this standard were included. A comparison of schizophrenic patients receiving Vitamin D (daily dose: 500–1000 i.u.) with those not receiving this vitamin revealed a significantly lower urinary excretion of phosphate by the former and so patients receiving Vitamin D were excluded from this study.

Figure 1 presents the mean rate of urinary phosphate excretion during the various collection periods of the fed and fasting studies. In neither study was there any statistically significant difference between the catatonic and paranoid patients.

In the 7:30–11:30 a.m., and the 11:30 a.m.–3:30 p.m. periods during the fed experiment (Figure 1a), the schizophrenic group had a lower ($P < 0.05$) output of phosphate than the normal group. During the other periods there was no significant difference in phosphate excretion between the normal and schizophrenic groups. Nevertheless, the output of the catatonics and paranoids was always less than that of the normals and as shown in Table 1, the total 24-hour excretion of phosphate of the combined schizophrenic group was significantly less than that of the normal group.

In the fasting study (Figure 1b) the normal subjects did not show the sharp increase in phosphate excretion during the day that they had in the fed study. Thus they did not differ significantly in their diurnal pattern or total output of phosphate from the schizophrenic subjects.

The present results for the urinary excretion of phosphate during the morning of the fed day are generally lower than those reported in our previous investigation (6). They are, however, similar to those reported by others (2). In our earlier study a low urinary excretion of phosphate was evident only in the catatonic group, but now the paranoid patients also show this.

The phosphate output of the elderly-normals was approximately equal to that of the normals during the 7:30–11:30 a.m. period. During all the other periods their output was significantly lower. Indeed, it was significantly lower than that of the schizophrenics, except during the 7:30 a.m.–3:30 p.m. periods. A low urinary excretion of phosphate in older people has been observed by Hoagland (2). In our elderly-normal group (63–88 yr.) this low 24 hour output appeared to be related to the absence of an increase in output during the late morning and afternoon. A reduced intake and/or a reduced intestinal absorption of phosphorus could explain this lower output of phosphate in the elderly-normals. The fact that the phosphate output of the elderly-normals was also lower than that of the schizophrenics suggests that the difference observed between the latter and the normals may be due to differences in food intake. Estimation of the phosphorus intake of the schizophrenics from the hospital diet sheets and general observation of their food intake did not, however, support this supposition.

The paranoids showed a significantly greater output of phosphate only during the 3:30–7:30 p.m. period when they were receiving phenothiazine compared to when they were not (Figure 2). This change made the excretion pattern of this group similar to that of the normals. Phenothiazine therapy

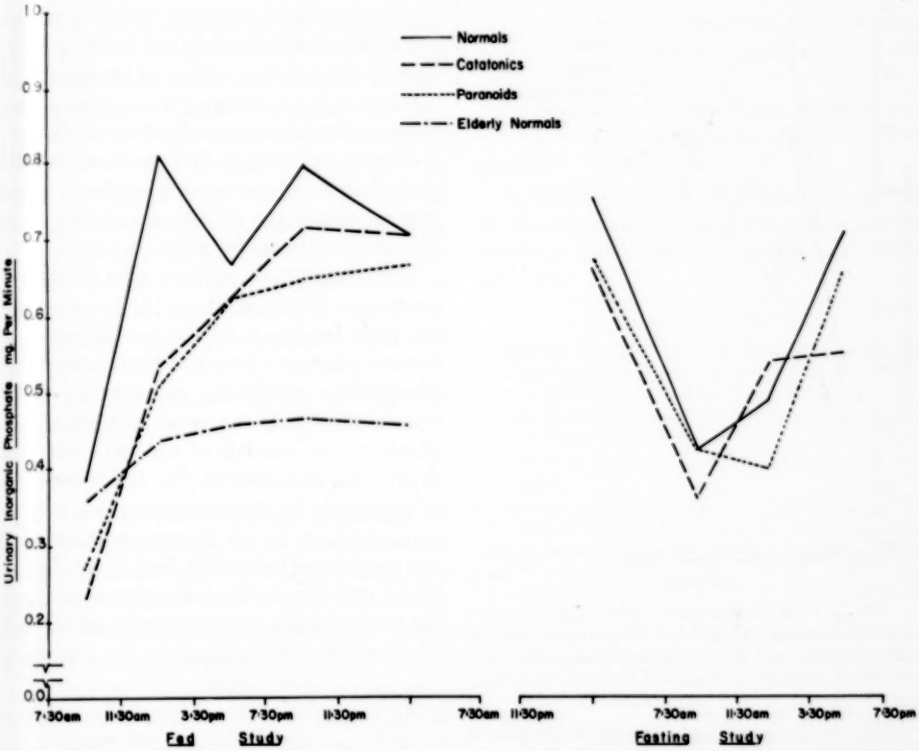

FIG. 1a. Diurnal variation in the urinary excretion of inorganic phosphate by healthy orderlies (normals), older men under custodial care (elderly normals) and paranoid and catatonic schizophrenics. The periods of urine collection were 7–11 a.m., 11 a.m.–3 p.m., 3–7 p.m., 7–11 p.m. and 11 p.m.–7 a.m. The subjects ate ad libitum during this study.

FIG. 1b. Diurnal variation in the urinary excretion of inorganic phosphate by the same groups, except for the elderly normals, as shown in Figure 1. The subjects received nothing to eat from 6 p.m., immediately before the urine collection, until the study was completed except for 163 calories and 23 mg. of phosphorus during the daytime.

TABLE 1

Urine and Serum Phosphate and Urine Volume of Schizophrenic and Normal Subjects

Group	N	Urine		Serum
		Volume ml./24 hr.	Inorganic Phosphate (P) mg./24 hr.	Inorganic Phosphate (P) mg./100 ml.
Fed Study				
Normal	7	1598 ± 202*	984 ± 66.6	3.50 ± 0.12
Schizophrenics	20	1275 ± 123	830 ± 32.1	3.52 ± 0.14
Catatonic Schizophrenics	8	1553 ± 279	854 ± 65.2	3.58 ± 0.21
Paranoid Schizophrenics	12	1089 ± 97	814 ± 33.1	3.49 ± 0.19
Elderly Normals	10	1763 ± 159	638 ± 72.2	3.45 ± 0.17
Fasting Study				
Normals	10	1873 ± 376	1002 ± 60.9	3.47 ± 0.12
Schizophrenics	15	1308 ± 134	806 ± 39.3	3.33 ± 0.12
Catatonic Schizophrenics	6	1649 ± 247	773 ± 43.3	3.40 ± 0.24
Paranoid Schizophrenics	9	1119 ± 124	824 ± 57.1	3.30 ± 0.14

* Mean ± S.E.M.

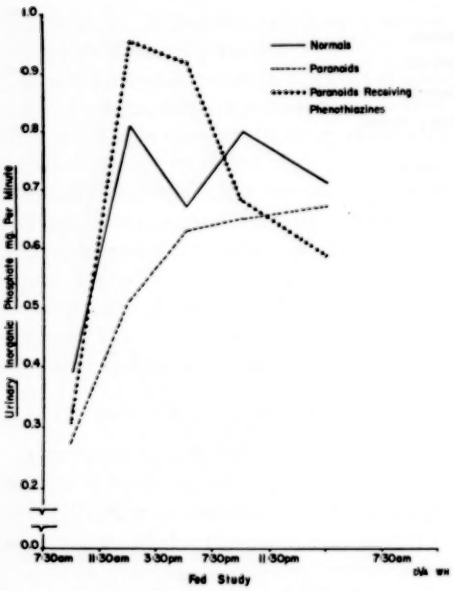

FIG. 2. Diurnal variation in the urinary excretion of inorganic phosphate by paranoid schizophrenics with and without phenothiazine therapy. All subjects received food and fluid ad libitum.

produced no significant changes in output of phosphate by the catatonics (Figure 3). We are unable to offer an explanation for this apparent difference in response to phenothiazines between the paranoids and catatonics.

The 24-hour urine volumes of the several groups are also compared in Table 1. Polyuria has been observed in schizophrenics (1) and this was apparent, particularly in the paranoids, in our previous investigation. This time, however, the schizophrenic patients showed no tendency to polyuria and, indeed, in the fed study the urinary output of the paranoids was significantly ($P < 0.05$) less than that of the normals.

The concentration of serum phosphate may vary rather widely between individuals and in the same individual from time to time. There were no significant differences between the mean concentrations of the several groups in this investigation.

To determine that the difference in inorganic phosphate excretion between schizophrenics and normals was not due to a difference in the relative output of inorganic and total phosphate, the urine was collected from eleven schizophrenics and five normals, from 7:30 a.m. to 7:30 p.m. and analyzed for total phosphorus and inorganic phosphate. There was no significant difference between these two measurements in either group.

The exclusion of subjects who deviate by more than 10 per cent from the mean weight for their height or who are receiving some therapy such as Vitamin D which may affect phosphorus metabolism reduces the difference in phosphate excretion between schizophrenics and normals of the same age, but it does not eliminate it. The lower excretion of phosphate by the schizophrenics is not due to a variation in the proportion excreted in the conjugated form. The daily cycle of phosphate excretion in the schizophrenics is similar to that in the normals except for the lack of a marked excretion peak in the late morn-

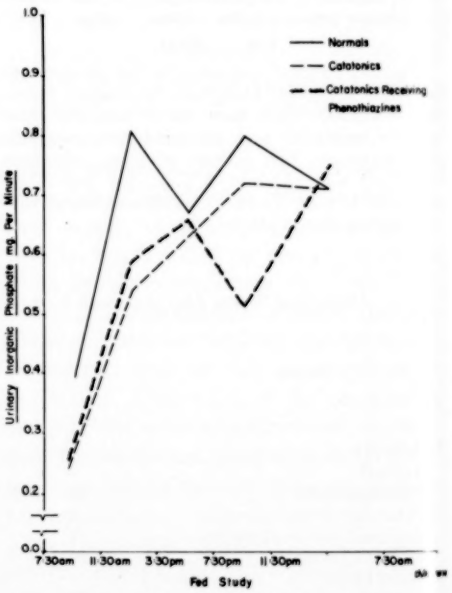

FIG. 3. Diurnal variation in the urinary excretion of inorganic phosphate by catatonic schizophrenics with and without phenothiazine. All subjects received food and fluid ad libitum.

ing. This peak is absent in the normals when their food intake is severely restricted. The foregoing observation, and the fact that the elderly-normal subjects excreted even less phosphate than the schizophrenics suggests that a low intake of food, or of phosphorus, may be responsible at least in part for the low output observed in the schizophrenics. The estimated food intakes of the schizophrenic patients do not lend support to this concept, however. On the other hand, intestinal absorption is known to decrease with age and this may occur earlier in the hospitalized schizophrenic than in the ordinary population.

SUMMARY

1. Paranoid and catatonic schizophrenic patients excreted less urinary phosphate than healthy normal subjects of similar age but more than elderly normal men. There was no significant difference between the paranoid and catatonic groups.

2. Neither the schizophrenic nor elderly-normal group showed the marked peak in phosphate excretion during the late daytime shown by the normal men.

3. The administration of phenothiazine drugs resulted in an increased daytime peak of urinary phosphate in the paranoid but not in the catatonic group.

4. There were no significant differences in the levels of serum phosphate in the various groups.

5. The low output of urinary phosphate by the schizophrenics may reflect a decreased intake or absorption of phosphorus by these patients.

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TOFRANIL (IMIPRAMINE) IN THE TREATMENT OF DEPRESSIVE STATES[1]

WOLFRAM KEUP, M.D.,[2] ARNOLD APOLITO, M.D., LEON OLINGER, M.D., MILTON SCHWARTZ, M.D. AND ELEANOR YACHNES, M.D.

When Marsilid (iproniazid) was introduced into psychiatric therapy (2, 10), undesirable side effects were soon reported. Since t is believed that the antidepressant effect of iproniazid is related to its action as a monoamine oxidase (MAO)-inhibitor, other MAO-inhibitors less toxic than Marsilid were tried with depressed patients. Nevertheless Marsilid seemed to be the most effective substance within this group. The assumption that MAO-inhibition and antidepressive effects are related is based mostly on the facts that 1) most known MAO-inhibitors elevate the serotonin level in the brain and have antidepressive effects, and that 2) reserpine and related drugs are known to lower the serotonin content in the brain by freeing it from its tissue-bound form, sometimes producing mental depression. The mechanism of such a supposed linkage is unknown, and at the present time it seems to be probable that amines other than serotonin may be more important.

In 1957 Kuhn (7) published his first results with the new antidepressive drug Tofranil (G-22355, Imipramine), which was found to be a non-MAO-inhibitor. Except for this attribute, the biochemical mechanism of Tofranil is unknown.

Tofranil is an iminodibenzyl-derivative. Its structural formula (Figure 1) is close to that of Promazine, but it does not contain a phenothiazine ring since the sulphur is substituted by a $—CH_2—CH_2$-bridge, forming a dibenzazepine nucleus. This changes not only the structural formula, but also the stereoformula. Pharmacologically, it retains some of the properties of the phenothiazine-tranquilizers: 1) it does not produce psychomotor agitation in experimental animals, and in high doses (10–30 mg./kg. intraperitoneally) has a sedative effect; 2) barbiturates are slightly potentiated; 3) it has a blocking effect on parasympathetic synapses; 4) it has demonstrable atropine-like effects; 5) it has a weak anesthetic and analgesic effect; 6) it induces a transient fall in blood pressure in the anesthetized cat; and 7) it has a spasmolytic effect in the isolated intestine (5, 8). The difference in action on MAO suggests at least a slight difference in clinical action if MAO-inhibition is involved in the antidepressive effect. Voelkel (15) supposed that Tofranil is more indicated in overactive and agitated depressed patients because of its mild tranquilizing effect, and that Marsilid-like compounds on the other hand are more active in apathetic underactive depressed patients. This opinion was not generally accepted during the discussion at Rome in 1958.

A double-blind study was therefore proposed, to compare Tofranil with one of the MAO-inhibitors less toxic than Marsilid. However, to date we have not found a psychoenergizer potent enough to be compared with Tofranil, and accordingly have decided to give the present preliminary report about Tofranil alone, to the end of encouraging the use of this drug in State hospitals, and of encouraging research into its mechanism and its specific psychological action.

MATERIAL AND METHOD

Sixty-six unselected depressed patients with different diagnoses, largely endogenous depressions, were observed during their

[1] This article was presented in part at the Downstate Interhospital Conference, New York, April, 1959.

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treatment with Tofranil[3]. The age of the patients, 28 male and 38 female, ranged from 25 to 72 years. About one-third of these patients were chronically depressed. The patient group had already been hospitalized for periods of time up to five years (average three years) and half the group had a history of previous hospitalization. Some of these patients had been pretreated with electroshock, insulin-therapy, and different tranquilizing drugs without reported effect. The patients were not under intensive psychotherapy during this study.

Dosage: Oral administration only was used since no fundamental difference between oral and parenteral application has been reported (13, 14). Treatment was usually started with a dosage of 75 mg. per day, and was increased slowly up to a mean dosage of about 200 mg. per day, individually adjusted. In some cases higher doses were used, up to 400 mg. per day. Doses up to 600 mg. per day have been reported to be tolerated by other authors (3, 4, 8). Lehmann *et al.* (8) reported having seen an increasing number of side effects with doses of over 200 mg. daily.

It is believed (1, 3) that a prolonged treatment with a low maintenance dosage is necessary to prevent relapses. It has not yet been established whether a depressive episode is actually shortened or is merely suppressed by the drug (7). Therefore, we used long-term treatment, for periods up to five months. In some cases combination with a tranquilizing drug was indicated because of impending agitation or disturbance of sleep. Thorazine was added in seven cases, reserpine in two.

Evaluation: Each patient was seen daily by two psychiatrists who made independent weekly evaluations of the results of treatment in every case. At the end of the study all of the recorded observations were reviewed, and a final evaluation of the degree of improvement in each case was agreed on.

[3] Geigy Pharamaceuticals, Yonkers, New York, generously made available a supply of the drug for this study.

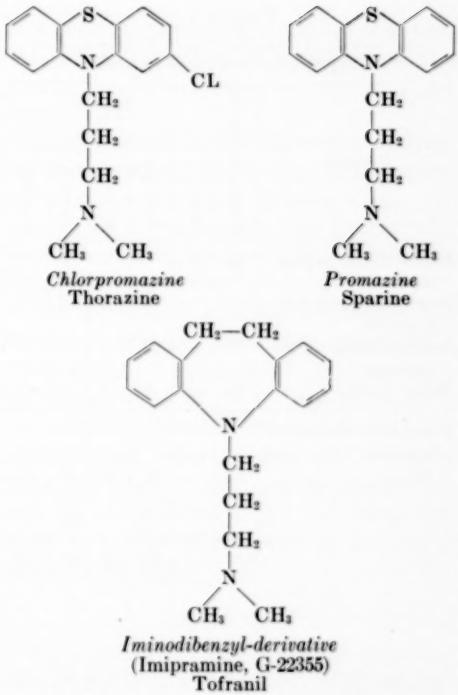

FIG. 1. Structural formulas of Thorazine, Sparine and Imipramine.

RESULTS AND DISCUSSION

The overall results in the different diagnostic groups are shown in Table 1. The group labeled "other types" represents patients with senile and arteriosclerotic depression, and one case of neurotic depression.

The results in endogenous depressions were distinctly better than those in schizophrenic and other types of depression, and statistical analysis showed that this difference was highly significant ($t = 3.67$; $P < .01$), thus confirming the findings of other authors (4, 7, 8). The best response in depressions of the endogenous type was obtained in involutional depression, with 24 improvements against four unchanged patients, but the number of patients with involutional and manic-depressive depressions

TABLE 1

Total Result of Treatment with Tofranil in 66 Hospitalized Depressed Patients

Diagnosis	Number of Patients	Result				
		Worse	Unchanged	Improvement		
				Moderate	Good	Recovery
Involutional depression	28	—	4	7	9	8
Manic-depressive depression	11	—	3	3	3	2
Schizophrenic depression	17	—	10	4	3	—
Other types	10	—	6	2	1	1
Diagnoses combined Number of patients:	66	—	23	16	16	11
				43		
%	100	—	35	24	24	17
				65		

was too small to show any statistically significant difference in their response.

Schizophrenic patients did not respond as well. None recovered, seven were slightly improved, and 10 remained unchanged. This confirms the data of Freyhan (4), Kuhn (7), Lehmann *et al.* (8) and Steck and Schneider (13). But we believe, as does Kuhn, that even a slight improvement in these patients justifies the use of this medication. Arteriosclerotic and senile depressed patients were also less improved in our material (7, 13). We could not confirm the good results of Tschudin (14) with this group of patients. Steck and Schneider (13) pointed out that in arteriosclerotic patients circulatory depression sometimes requires an interruption of treatment. In one patient we were forced to discontinue the drug because of a severe drop in the blood pressure. Our only case with neurotic depression recovered, but it must be noted that psychoneurotic patients usually do not react in a satisfactory way (1, 4, 8).

The rate of improvement in all diagnoses combined was 65 per cent, with 17 per cent total recovery. These figures are lower than those reported by some of the previous investigators: Steck and Schneider (13), 72 per cent; Lehmann *et al.* (8), 84 per cent. This may be due to the fact that our study includes a high number of chronically ill patients, who had been resistant to other methods of treatment. The improvement rate in endogenous depression alone (82 per cent) is much closer to the previously reported rate.

Table 2 shows improvement as related to psychiatric symptoms found in depressed patients. The highest proportion of improvement was seen in affective depression, but this did not differ significantly from the improvement of symptoms of "flow of psychological activity" and "alteration of thought process." In Table 1 the overall improvement, especially concerning depression, shows no worsening. However, some patients became worse in one or two single symptoms in spite of being less depressed. In nine patients impending or manifest agitation was observed. In eight of these patients this agitation could be counteracted by a tranquilizing drug, but in one patient even 800 mg. of Thorazine per day did not cut down the agitation and Tofranil had to be discontinued. We had the impression that latent psychotic contents were acted

TABLE 2

Influence of Tofranil on Symptoms Related to Depression in 64 Hospitalized Depressed Patients

Symptom related to depression	Result		
	Worse	Unchanged	Improved
Affective depression	1	22	41
Flow of psychological activity	1	28	35
Alteration of thought process	1	29	34
Psychomotor symptoms	9	24	31
Anxiety	2	30	32
Vegetative functions	1	32	31

out in this patient, although he was freed of his depression. The patient improved slowly after three weeks of Thorazine therapy.

Anxiety worsened in two patients. To keep the figures in Table 2 comparable, patients with no anxiety or no disturbance of vegetative functions, sleep, and nutrition prior to or during the treatment were listed as "unchanged." This must not be understood as "failure." Anxiety, mainly in psychoneurotic patients, was reported not to be influenced by Tofranil.

Side effects: As previously reported by other authors, the following minor side effects were observed: dizziness (three patients), nausea (one), blurred vision (two, perspiration (two), dry mouth (two), constipation (two). A slight drop in blood pressure was observed in a few patients, but in elderly patients this is sometimes actually a desirable side effect. It is, however, not a constant one.

Some of the side effects are seen only during the onset of treatment and disappear when therapy is continued. This holds true, too, for a slight tremor of the hands (six patients). In confirmation of Lehmann *et al.* (8), we did not observe other extrapyramidal symptoms, although Kuhn (7) did. No clinical signs of liver damage were seen.

The contention of Lehmann *et al.* (8), that side effects increase when more than 200 mg. of Tofranil are given daily, cannot be proved statistically by our rather small investigation, but we saw more agitation with higher dosage. The agitation in one of our patients was of a manic type (see Ref. 6), and the remainder of the eight patients showed an agitation with paranoid trends. No severe incidents were seen, and in general we agree with Steck and Schneider (13) that the side effects produced by Tofranil are of the same magnitude as, or even rarer than, those produced by many of the tranquilizing drugs. According to our experience, however, it is necessary to decrease the dosage of Tofranil and to add a tranquilizing drug immediately after the first signs of agitation are observed. When the tranquilizer is in full action, the dosage of Tofranil may be gradually increased again.

Improvement can be observed as early as the first or second day in some patients, but sometimes it takes two or three weeks. According to our experience, the patient who does not respond during the first three weeks will not respond at all.

The mechanism of action of Tofranil has been described as "progressive relaxation," "orthothymic," "euthymic" or "thymoleptic" rather than "euphoric." On the basis of our general impression we confirm that the psychological effect is definitely different from the effect of the "psycho-energizers" and the tranquilizing drugs, but we do not want to specify this impression without a double-blind study.

CONCLUSIONS

We believe that Tofranil is the most potent antidepressive drug available at the present time. While its potency is comparable to that of electro-shock therapy, and it certainly decreases the use of electro-shock, it will not replace electro-shock completely. The latency period before improvement occurs is considerably shorter with Tofranil than with the MAO-inhibitors, but is not as short as that of electro-shock therapy. So electro-shock may still be preferred in acutely suicidal patients. We feel that at the present time we have reached the point in mental depression where in most cases drug therapy should be tried first, and electro-shock may then be used if the drug does not act sufficiently well.

SUMMARY

The therapeutic results obtained with oral administration of Tofranil (G-22355, imipramine) in 66 depressed patients of different diagnostic groups (one-third chronically ill patients) and its action on different psychiatric symptoms related to depression have

been described. An overall improvement in 65 per cent of the patients was observed, while in endogenous depression alone there was improvement in 82 per cent. The various side effects observed in these patients, with emphasis on methods by which agitation may be prevented, were discussed.

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A LONG-TERM EVALUATION OF CHLORPROMAZINE IN SIX CHRONIC SCHIZOPHRENIC PATIENTS

PATRICIA NEELY WOLD, M.D.[1]

INTRODUCTION

Since the advent of the tranquilizers there have been varying opinions about the value of these drugs in the treatment of schizophrenia. Some investigators (6) have felt that they were of most value in institutions where personnel was limited, or with disorders that tended to be self-limited. There has been much emphasis on the necessity to separate placebo effect from that brought about by the medication (2, 9, 10, 17, 18, 20). Attempts have been made in some institutions, where both drugs and psychotherapy are used, to evaluate the relative effect of these two factors (15), but the issue is sometimes confused as to which is the more effective agent and opinions often vary with the bias of the physician (7). It has been stated by a number of investigators (4, 13, 14, 16, 21) that maintenance therapy is necessary. Reports of the period of time from the cessation of medication to the reappearance of symptoms have varied from twenty-four hours to six months (10, 21, 22, 23). Freeman and Cline (10) state that the effects of medication last four weeks and suggest intermittent therapy. Some have felt that the primary change was in the area of social behavior and that the "essential" disease was not changed (1, 5, 6, 8, 12, 19, 21); others have emphasized that in many cases the thinking processes do change and real insight is achieved (4, 10, 11, 13, 16).

This study is an attempt to isolate the chemical effect of one tranquilizer, Chlorpromazine, from the other factors possibly related to the shifting mental status of six chronic schizophrenic patients. An effort is made to arrive at some conclusion about the relationship between maintenance therapy and the quality of adjustment made by these patients.

PROCEDURE

Six female chronic schizophrenic patients were chosen for this study, all of whom had been inmates of a large mental institution where individual attention was minimal. All but one had been hospitalized five years or more previous to medication and all had relatives who were still actively interested in them. Five of the six had been treated in the hospital for periods of time varying from ten weeks to twelve months; one was medicated at the time of discharge. They were seen every three or four weeks for ten to fifteen minutes over a period of three and one half years, being told that the purpose of the visit was to regulate the dosage of medication. The dose was determined by the amount necessary to control symptoms. In two patients this averaged 400 mgm. daily, in two it was 100 mgm. daily, in one 300 mgm. and in one 50 mgm. (this was the patient who did not require continued medication). The drug was furnished free of charge and routine monthly white counts were insisted upon during the entire three and one-half year period. A great deal of emphasis was placed on the value of the medicine and any dynamic interpretations were avoided.

When each patient had been out of the hospital for one year, she was given a supply of placebos in place of Chlorpromazine.

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Notes were made on important events in the patient's life as told by the patient or a relative; likewise symptomatology was judged both by the verbal report of the relative and observation in the interview.

When the patient was obviously experiencing a relapse, she was told that the dose of the "medicine" would be raised. Relatives and patients were encouraged to feel that this was the solution. The patients were hospitalized when necessary; none of the personnel except the director of the hospital was aware that they were on the project. The patients were medicated with Chlorpromazine while in the hospital and were discharged as soon as their mental status was judged the same as before the placebo had been given.

The placebo was instituted a second time when the patients had clinically improved to the pre-placebo level as reported by their relatives or as evidenced by their obtaining employment.

RESULTS

Six patients were studied all of whom had been diagnosed as chronic schizophrenia at the onset of the investigation. All six had responded to treatment with Chlorpromazine. Two had been hospitalized five years previous to discharge, one, one and one-half years, one seven years, another nine years, and the last ten years. At the time that drug therapy was started five presented the typical picture of chronic schizophrenia including flatness of affect and bizarre ideation. The sixth had a minimum of schizophrenic features, the psychosis consisting mainly of paranoid ideation which did not have a bizarre quality. The study began at the time that the patients were discharged. Their ages at this time were 33, 37, 38, 38, 41, and 42 ($M = 37.2$).

Five of the six patients responded to the institution of a placebo with a major relapse involving severe social disorganization. Since the experiment was repeated twice for each patient, this represents a total of ten instances in five patients in which giving a placebo was followed by a notable and major relapse.

The patient who presented the picture of a paranoid psychosis without the marked disorganization of schizophrenia did not react to the placebo and medication was discontinued. She showed no signs of relapse for the next seven months.

Among the five patients who relapsed, the period of time between institution of the placebo and the relapse varied widely. It was noted, however, that the interval was remarkably consistent for each patient when the experiment was repeated. The intervals were five days, eighteen to twenty days, two months, four and one half to five months, and five months. The length of the interval was not related to the dosage.

The major relapses did not seem to be related to events in the patient's life. This was exemplified by one case whose first relapse seemed to coincide with interpersonal tension with a brother. When Chlorpromazine was reinstituted, however, she was able to handle this. It appeared in another case that interpersonal tension with her employer was related to the form of the hallucination in that the patient heard a voice calling her a "loud mouth," the term she used to describe the boss. This occurred while she was on Chlorpromazine, but the symptom lacked the severe disorganization of the placebo relapses. This was the patient who proved the most difficult to keep adequately medicated because of her tendency to reduce the dose herself. This may have been why she hallucinated from time to time while on the drug.

When medication was reinstituted, subjective improvement preceded that reported by the family in four cases. The period of time necessary for the patient to reach the pre-placebo level of behavior was of roughly the same magnitude as the length of time required for the relapse to become full blown.

There was a characteristic and reproducible order of symptoms for each patient

when the placebo was given, sleeplessness and tiredness being the first in three cases. Then followed inability to maintain employment, unkempt appearance and hallucinations. In another, the first symptom was withdrawal, followed by antagonism to fellow employees, and hallucinations, resulting in a loss of job. The fifth patient's first symptom was irritability and antagonism, followed by inappropriate behavior. The same symptomatic sequence was repeated with each patient in both relapses.

DISCUSSION

Although this study did not follow the double blind technique, and although some, perhaps all, of the patients were aware that they were receiving a different pill (not as far as is known, a placebo), it is difficult to explain the individually consistent and widely varied relapse periods on any basis other than a response to the widthdrawal of the Chlorpromazine. The relapses occurred in the five patients despite the fact that positive feelings for the treating physician were encouraged and seemingly maintained as well as faith in the pills). Since formal insight psychotherapy in any sense other that a positive feeling for the doctor, was excluded, it would seem unlikely that this was a factor. The possibility of spontaneous remission would seem to be remote because of the patients' chronicity. The evidence suggests, then, that the relapses were related solely to the withdrawal of Chlorpromazine.

The rather surprising finding that the patients had an individually consistent relapse period which was different in each case, must help to account for the fact that studies of the reaction of schizophrenics to drugs or other chemicals, involving groups of patients have been so inconclusive and the results so varied. This finding must be taken into consideration in evaluating treatment in institutions where both psychotherapy and tranquilizers are used, since the relation between cessation of the drug and relapse may be obvious only in patients with short relapse periods. When the relapse period is of several months duration, it may well coincide with a change of personnel or emotionally significant event in the patient's life on which the regression is blamed.

The characteristic feature of the placebo relapses seems to be severe social disorganization. All five patients were neither able to maintain relationships with the people in their lives nor to remain employed. These features were prominent with all ten relapses. The extent to which the mental processes were altered varied; at times the voices were heard, at other times not, but the patients seldom recognized that they had been hallucinated. (This was not true of the patient with the paranoid psychosis; she later felt that her accusations of her husband were unfounded.) However there appears to be little doubt that the medication made the difference between hospitalization and being self-supporting in the five patients who presented the more disorganized picture. Kris and Carmichael (14) in a long-term follow-up study of chronic schizophrenics maintained on Thorazine suggest that indefinite drug therapy is necessary. The present study, which was conducted over a period of three and one half years, would tend to confirm their viewpoint.

The results of this study suggest that there is a group of chronic schizophrenic patients which requires medication with Chlorpromazine in order to remain in the community. Further studies are needed to discover whether or not this is also true of certain acute schizophrenic patients. The evidence suggests that although interpersonal tensions may alter the form of the distortion of reality, these same tensions can be handled without distortion when the patient is adequately medicated, and that therefore they are not the predominant factor involved in relapses in this type of schizophrenia. Since in this study two cases took as long as five months after the substitution of a placebo for Chlorpromazine to reach the point where hospitalization was indicated,

it would seem important that very careful histories of drug treatment be taken with any patient returning to the hospital.

SUMMARY

Six chronic schizophrenic patients being maintained with Chlorpromazine were treated on an outpatient basis. It was found that five of the six patients responded to a placebo with a major relapse. Each patient had a characteristic and reproducible period of time from the institution of the placebo to the relapse. The relapses did not seem to be related to significant life events.

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THE TREATMENT OF SCHIZOPHRENIA WITH SUSTAINED EXPOSURE TO HEXAFLUORODIETHYL ETHER

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Since 1957 hexafluorodiethyl ether (Indoklon[3]) has been used at The Spring Grove State Hospital as an inhalant convulsant in the treatment of psychiatric disorders requiring convulsive therapy (1–3, 5, 6). Studies comparing Indoklon with ECT indicated no significant difference in clinical results. As the safety of this procedure was demonstrated by the administration of over 1500 individual treatments in 125 patients without any serious sequelae or complications, it became of interest to determine the effect of a series of repeated exposures within a period of five to 15 minutes.

Preliminary to this investigation a study was carried out by Krantz and his coworkers (4) on animals using this technique. These studies indicated that animals could be given repeated exposures to Indoklon for as long as 30 minutes with no serious complications observed in the post-convulsive behavior of the animal or evidence of any toxicity as indicated by blood and urine studies. Subsequent sacrifice of the animals, namely monkeys, dogs and rats, revealed no gross or microscopic damage in the viscera or the brains examined. Metabolic studies revealed that the compound was excreted unchanged by the lungs, indicating that its anesthetic and convulsant action are probably related to some type of reversible biochemical process in the brain.

Having demonstrated the relative safety of the procedure, eight schizophrenic female patients were selected for a trial on this type of treatment. These were patients who had been hospitalized for one year or more and were considered to have a very poor prognosis. They had been exposed to a program of treatment that included tranquilizing drugs, electroconvulsive therapy, insulin, and various forms of individual and group therapy with little effect on the course of their illness.

The study of the patients in preparation for this treatment included a physical examination, x-ray, EKG examinations and routine blood and urine tests. They were prepared for treatment in the usual manner and breakfast was withheld. One mg. of atropine sulfate was administered intramuscularly about 15 minutes before treatment. The patient was then given Indoklon by inhalation through a modified Stephenson mask as described previously (1, 3). As soon as the patient's respiration was observed to return to normal after the induction and termination of the first seizure, the inhalant was reapplied and another seizure produced. Occasionally some cyanosis occurred; at this time the patient was ventilated with oxygen for a few seconds until normal color was restored and treatment continued. This pro-

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[3] Trade name: Indoklon. Supplied by the Ohio Chemical & Surgical Equipment Co. (A Division of the Air Reduction Co., Inc.), New York. This investigation was supported in part by Research Grant MY-3048 from the National Advisory Mental Health Council, National Institutes of Health, U.S. Public Health Service, administered by Friends of Psychiatric Research, Inc., Baltimore, Maryland.

TABLE 1

Patient R. B. (Eighth Treatment)

Time of exposure	40″	45	45	35	0	30	0	30	10	0	30	0	0
Number of seizure	1	2	3	4	5	6	7	8	9	10	11	12	13
Duration of the seizure	55″	40	30	15	25	20	25	65	25	30	35	20	20
Interval between seizures	15″	15	35	10	20	120	15	10	25	5	10	5	

Total time of exposure to Indoklon vapor	4 min. 25 sec.
Total number of seizures	13
Total time of duration of seizures	6 min. 45 sec.
Total time between seizures	4 min. 45 sec.

cedure was cautiously repeated, gradually increasing the number of seizures during each treatment procedure in order to observe the subsequent clinical course.

The data relative to the treatment procedure were recorded as follows (with all times being recorded in seconds): a) exposure time; (this was considered to extend from the time of application of the convulsive inhalant to its removal at the onset of the seizure; b) the number of seizures; c) the duration of the seizure (from the onset of the eyelid twitchings through the tonic state to the termination of the clonic muscular jerks; and d) the interval between the termination of a seizure and the readministration of Indoklon. (During this time the patient always remained unconscious.) A typical example is the record obtained during patient R.B.'s eighth treatment as outlined in Table 1.

The phenomena observed relative to the time of exposure were consistent throughout the treatment for all the patients in the study. The time of exposure to Indoklon required to produce a seizure decreased with successive seizures as treatment was continued until a point was reached where the patient would convulse spontaneously without further application of the gas (indicated by a zero in the table) within 10–20 seconds after previous seizure. This would occur only once or twice and reapplication of the inhalant was usually necessary to induce further seizures. (It should be noted that the number of seizures was limited to 13 or fewer in this investigation and the total exposure time to the inhalant did not usually exceed three or four minutes.) There was some slight variability in the time of exposure from patient to patient, probably as the result of a difference in the fit of the mask, but on the whole there was a marked consistency in the time required to induce convulsive episodes.

The duration of the seizures tended to diminish as seizure followed seizure. It was also observed that the induction time diminished in the same manner. The longer duration of the initial seizure could be regained by allowing an interval of 60–120 seconds of normal breathing to occur between the seizures. However, a treatment was continued there was again the shortening of the time of application necessary to induce a seizure, again with a decrease in its duration.

The interval between seizures was characterized by the return of the regular respiratory excursions, although the patient remained unconscious. The treatments were followed by a marked diminution of the usual immediate post-convulsive psychomotor excitement.

The number of seizures during any one treatment was limited to a total of 12 or 13. This was based on the observation that as the number of seizures was increased from one to four, the patient recovered from the effects of the treatment in an hour or two. Administration of from four to eight seizures resulted in the patient's becoming quite lethargic and spending the remainder of the morning in bed, usually missing the noon meal because of a slight feeling of nausea. When the patient had received eight to

TABLE 2

Summary of Data on Series of Eight Patients

Patient	Age	Pres. adm. in months	Symptoms	Seizures: Number obtained during each treatment; Interval between treatments in days	Total Seizures
1. R.B.	33	20	Withdrawn, catatonic, mute, blocking, grimacing, suspicious	3 6 6 5 6 10 12 13 7 1* 6 9 1* 1* 2 19 2 5 16 14 7 7 7 2 2 2 7	86
2. S.B.	37	20	Many somatic complaints; depressed, seclusive; potentially suicidal, delusional	5 6 2 4 3 3 7 6 2 4 2 4 4 4 4	36
3. N.K.	28	12	Delusional, hallucinated, hyperactive, apprehensive, extreme emotional lability, denudative, exhibitionistic	4 3 3 4 5 8 5 6 12 10 16 2 2 2 4 4 2 2 4 15 7	76
4. G.J.	30	72	Hallucinated, periods of intense excitement, soils self, completely out of contact, eating excreta and inserting foreign bodies into body orifices	5 2 5 6 2 10 10 8 12 11 8 1* 1* 1* 2 2 4 2 12 9 5 9 7 3 18 7 6	82
5. E.M.	38	26	Hallucinated, delusional, agitated, hyperactive, confused, speaks incoherently	7 5 7 11 5 7 2	30
6. E.F.	39	17	Delusional, agitated, restless, push of speech, flight of ideas, irrelevant, some confusion and depression	6 4 5 11 6 1* 7 1* 6 5 6 6 5 29 7 14 7 5 2 17 2 2 3	64
7. A.R.	32	17	Hallucinated, suspicious, evasive, negatavistic, psychomotor retardation, blocked and depressed	7 13 9 8 1* 6 6 6 6 5 7 5 7 26 7 2 5 19 2 2 3 2 3	79
8. M.S.	30	18	Seclusive, withdrawn, hostile, hallucinated, catatonic, mute and stuporous	12 11 6 8 1* 1* 6 6 6 7 6 6 2 5 2 2 7 3 14 2 2 3 2	76

* Administration of Indoklon by an intravenous technique (to be discussed in a later paper).

12 seizures the patient remained in bed most of the day with an increased feeling of nausea and occasional vomiting. However, the next day the patient experienced no untoward effects.

The data of the investigative experiences with the eight patients are outlined in Table 2. It will be noted that the prolonged exposures were administered as a symptomatic treatment with no definite time interval set between treatments or any definite number of treatments (see Table 2). In the absence of any information as to the cumulative effect of such treatment, it was thought best to proceed with caution.

The number of seizures administered ranged from 30 to 79 in the patients in this study, given over a period of one to three months with gaps of two to 21 days between treatments. The patients appeared to feel the same apprehension about taking this treatment as they did about electroconvul-

sive therapy. However, there was no memory for the treatment procedure, except for the initial application of the mask. The response to treatment in this group of patients was minimal although it was observed that following the first to the first three treatments the patients displayed a rather moderate symptomatic improvement which was not maintained with continued treatment. However, as indicated, the irregularity with which treatment was applied plus the extremely poor prognosis of the patients in this study may well have contributed to the negative results. No serious complications were observed as a result of the treatment and no untoward reactions were noted in the few months which have followed cessation of treatment in these patients. Several have since shown some spontaneous improvement in their symptomatology.

The following two cases (Pt. #1, R.B. and Pt. #6, E.F.) are presented to illustrate their response to treatment and their clinical course.

Case History, Pt. #1, R.B. A 33 year old white married female was admitted to the Spring Grove State Hospital in April, 1957. At time of admission she was confused, restless and very suspicious. She smiled inappropriately, at times seemed catatonic, and verbalizations were limited to a perseverating type of questioning being repeated over and over as to when she would get out of the hsopital. At the same time she displayed little awareness or concern relating to her symptomatology. The diagnosis of schizophrenic reaction with paranoid and catatonic features was made.

She was placed on Thorazine with no particular improvement and then was given a course of Indoklon convulsive therapy in 1957 with a moderate degree of improvement. At that time she was given 12 Indoklon treatments with one seizure being administered at each treatment. There was a moderate degree of improvement and she was released from the hospital on parole. She was maintained on the phenothiazines and attended the out-patient clinic for several months. In April, 1958, she was returned to the hospital in a semi-catatonic state manifested by blocking, grimacing, withdrawal and muteness. This state persisted and in September, 1958, she was placed on a course of sustained exposure to Indoklon. Following the second treatment she showed moderate improvement in that she was not as mute, blocked and seemed less catatonic. She started to relate to the other patients in a friendly manner and continued to express desires to go go home for a weekend with her husband.

Because of the rather moderate improvement it was decided to wait before continuing with further treatments to obtain some idea as to how long this improvement would be maintained. The improvement was maintained for about three weeks and then she began to display her previous symptomatology of increasing withdrawal, suspicion, some muteness with repetitive verbalizations concerning a desire to go home. She was given her third treatment; in the following five days she displayed improvement similar to her previous state and developed an episode of euphoric behavior in which she smiled a great deal and became rather voluble and active in participating in ward routines. Three weeks later there was a recocurrence of her regressive behavior and she received a fourth treatment, and a week later a fifth, with little change in her catatonic state. She then was given a weekly treatment for the next four weeks with little change in her status.

Treatment was continued until she had a total of 12. At that time she was described as eating and sleeping well, talked a little more but still made the same verbal demands to go home and tried to elope whenever she got the opportunity. She spoke of having some difficulty in sleeping. On the whole there seemed to be only a minimal degree of improvement.

Case History, Pt. #6, E.F. This is a 38 year old white female admitted for the third time in June, 1958. She had been initially hospitalized in 1945 with her first psychotic episode. She received ECT, improved and was released. She subsequently had several psychotic episodes following the birth of her children in 1947, 1949 and 1950. Not all of these episodes necessitated hospitalization. In 1952 she was again hospitalized and at that time was diagnosed as schizophrenic. She received another course of ECT but did not show much progress. The patient was placed on Thorazine and ultimately released. In 1956 she was admitted again. During her parole she had continued to make a marginal adjustment in the community but then had become upset, agitated, displayed restlessness, blocked, had a rush of speech, flight of ideas, and displayed some mental confusion. On this admission she was tense, confused, preoccupied, dissociated and appeared somewhat depressed. The diagnosis was then made of schizophrenic reaction, schizo-affective type.

The patient was placed on treatment receiving sustained exposure to Indoklon. After her first

treatment she was described on return to the ward as appearing restless, confused, and talking incoherently. She complained of headache, nausea and refused lunch. The patient went to bed and rested quietly; by midafternoon she was her usual self. Two days later she received her second treatment with the same sequence of events. The following day she was described as being much less talkative; she was able to sit still longer and seemed to be speaking more rationally. In interview she spoke in a slow, relevant, coherent manner. She expressed concern about herself, her family and the problems at home. She mentioned that she had had ECT before, a great deal of it, and that she somehow had the feeling this treatment was less threatening to her. She also mentioned that she had been receiving Thorazine for a great many weeks without any particular effect as far as she could tell, but then the treatments seemed to help her more. (By treatments she was referring to the Indoklon.)

Treatment was continued with this patient after an interval of a month because she had begun to display evidence of regression, in that she was becoming tense, suspicious, with increasing psychomotor activity, and her thinking was becoming more dissociative. As treatment continued there would be an improvement for a few days after a treatment with a gradual return to her previous state.

DISCUSSION

Since this study was exploratory in character, the data are primarily experiential. It was from this point of view that the following observations in the treatment of the patients were made. After the second or third treatment varying degrees of symptomatic improvement occurred, but were not sustained. Additional treatment occasionally produced transient euphoric states, only to be followed by an intensification of the regressive symptomatology. At present, the investigators have no explanation for these fluctuations.

While it seems desirable to compare this treatment with other modalities of convulsive therapy and their modifications, it would, however, seem premature to do so while there are so many uncertainties. Further studies are now in progress using a fixed number of seizures during one treatment period in patients with a more favorable prognosis. The results will be compared with patients receiving electroconvulsive therapy.

SUMMARY

Repeated exposure to the convulsant inhalant, hexafluorodiethyl ether (Indoklon) within the limitations of this investigation resulted in no serious sequelae or complications. Minimal or questionable clinical improvement was observed in a group of eight chronic female schizophrenic patients with extremely poor prognoses.

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A CLINICAL, ELECTROENCEPHALOGRAPHIC AND ANATOMICAL STUDY OF EXPERIMENTAL JAPANESE "B" ENCEPHALITIS IN THE MONKEY

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In spite of the fact that for many years there had been recognized in Japan spring and summer epidemics of a type of encephalitis accompanied by meningeal symptoms, frequently of fatal outcome, it was only in 1919, two years after the Viennese epidemic, that Japanese investigators compared this encephalitis to that of Von Economo.

Detailed clinical and anatomical studies were undertaken in 1924 during an extremely serious epidemic, and Kaneko and Aoki described precisely Japanese Encephalitis which they called "B," in order to distinguish it from the type "A" of Von Economo.

New epidemic outbreaks gave Takaki the opportunity to identify the virus, and also provided a clearer understanding of the anatomical lesions, due to the work of Mori, Kobayashi, Kaneko, Ogata and Mikaye. From the sometimes contradictory descriptions of Japanese authors, Bertrand and K. Miyashita deduced the idea of a simultaneous attack on the white and gray matter. Encephalitis "B" was considered to belong to the polioencephalitis group by reason of its severe neuronal lesions, and to the demyelinating encephalitis group because of the development of necrotic areas in the white matter and in the brain stem.

Hayashi demonstrated an experimental infection in the monkey six days following intracerebral inoculation, producing lesions analogous to those of human encephalitis.

During World War II and the Korean War, several outbreaks of epidemic encephalitis permitted new anatomical studies (Zimmerman 1946, Haymaker and Sabin 1947, Koide 1950), and the first electroencephalographic recordings were made (Shimoda and Fukuda, 1951; Radermecker, 1956).

In spite of the importance and diversity of studies of Japanese "B" encephalitis, it is evident that for the most part no anatomical studies have been supported by electrographic proof, and that the more recent electroclinical studies have not been verified by anatomopathological studies.

It is for this reason that we have undertaken experiments to study the correlations between 1) clinical symptomatology and changes in the electro-encephalographic pattern, and 2) the nature and topography of the anatomical lesions.

MATERIAL

This study is based on experiments with seven monkeys (Macacus Cynomolgus) provided by the Pasteur Institute of Saïgon. Monkeys 6 and 7 were 8 to 9 years old; five others were 3 to 4 years old; none of these animals showed symptoms of any illness prior to inoculation.

METHOD

The strain of virus used came from the laboratory of Dr. Nakamura (Tokyo), maintained by passage through mice according to the method of Reed and Munch. The duration of inoculation was five days. The preparation obtained from the mouse brains was kept at $-20°$ (C) for varying periods; 0.5 cc of a 1/10 suspension was injected into the fronto-parietal region of the right cerebral hemisphere.

Clinical observations of the animals could not be made continuously because of strict isolation of the animals and precau-

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tions taken to safeguard the attending personnel. Nevertheless, each animal was examined daily at feeding times and also when electroencephalographic recordings were made.

Recordings were made using an ALVAR electroencephalograph with six leads. The phonograph needle electrodes were implanted in the cranial vault at the time recordings were made. Four electrodes were implanted longitudinally on each half of the skull: one frontal, one central, one parietal, and one occipital. Only the bi-polar method was used. Recordings were made from each animal once or several times between the time of inoculation and the onset of symptoms, and once or twice daily from this time on.

The animals were sacrified between the fourth and eighth day following inoculation; no serological control was carried out, but in two animals cortical specimens were taken and mice were inoculated with them. The reactions of these mice demonstrated the usual virulence of the strain.

The nervous system was fixed in 15 per cent formol; ten sections were made anteroposteriorly at the level of the hemispheres in the fronto-vertical plane and three or four at the level of the brain stem in the horizontal plane. Each of these fragments was dehydrated slowly, embedded in paraffin after passage through chloroform. The blocks were cut in their entirety; one section in twenty was mounted; staining was carried out using the following methods: haematoxylin-eosin, Masson trichrome, Nissl, cresyl violet, Glees and Loyez.

RESULTS

Monkey #1. An animal aged three to four years was inoculated on 24th September, 1955, and received 0.5 cc of an 8-day old 1/10 suspension. The animal was sacrificed four days after inoculation, before the appearance of any clinical manifestations of disease.

The electroencephalogram was checked on several occasions and was always within normal limits.

The lesions studied showed a generalized cerebral edema with perivascular, subarachnoid, and periependymal involvement (Figure 1). In the white matter there appeared multiple peri-oligodendroglial vacuoles and small spongy areas with adjacent discrete astrocytic reactions with clear nuclei. Associated with this were scattered evidences of neuronal and axonal involvement without inflammatory lesions of a productive type.

Monkey #2. An animal aged three to four years was inoculated on August 13, 1955, and received 0.5 cc of a 1/10 suspension 15 days old. First clinical manifestations of disease appeared on August 20 after an incubation period of six days. The animal sat in a corner of his cage, sometimes lying down; he maintained a certain degree of spontaneous movement; a left-sided hemiplegia with associated right-sided tremor was noted. The animal was sacrificed on August 21, the eighth day following inoculation.

Electroencephalographic findings: August 20; 5:30 p.m. (Figure 7A, upper). Tracings consisting of rapid background rhythms of low amplitude without alpha waves. Slow theta and delta waves occurred either isolated or together in a fusiform burst, bilaterally synchronous, with a posterior predominance. These waves disappeared when the animal opened its eyes. There were present, in addition, slow spikes of great amplitude focalized to the central area of the right hemisphere (the site of inoculation) where they occurred sporadically or grouped in a pseudo-rhythmic manner.

August 21; 2 a.m. (Figure 7B, upper). The tracings were aggravated by the disappearance of the rapid background rhythms and they were replaced by a slow continuous delta and theta dysrhythmia. The slow bisynchronous waves predominated in the anterior regions and were not blocked when the animal opened its eyes. The spikes previously recorded on the right hemisphere had disappeared.

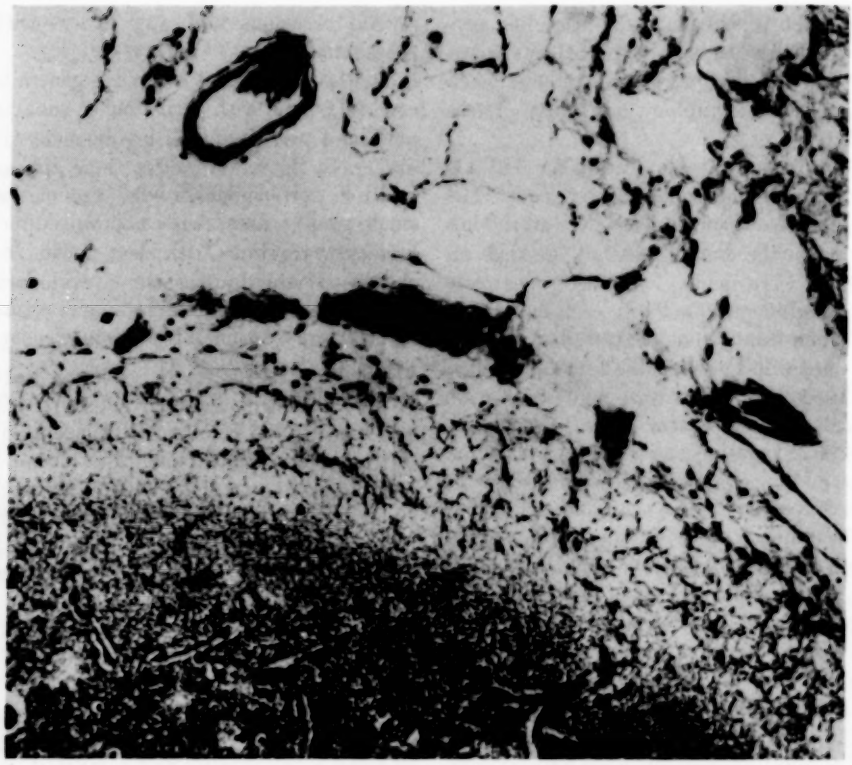

FIG. 1. Edema involving the lepto-meninges, and the molecular layer of the cortex which presents a finely vacuolar appearance (Monkey #1). It is this phase of the edema, however important, which does not express itself clinically nor electrographically and which is characterized by us, therefore, as the "latent" phase of encephalitis.

Anatomical findings: The lesions showed perivascular polymorphic cellular reaction (Figure 2A and B) composed of lymphocytes, mononuclear elements, some plasmocytes and histiocytic macrophages (Figure 2B). There were fewer perivascular infiltrations of a purely homogeneous lymphocytic nature. Observed as well were a diffuse or nodular gliosis (Figure 2C) and necrotic foci in the thalamus (Figure 2D). There was a generalized edema with vascular congestion, as well as neuronal and axonal changes with moniliform appearances. Superficially there was noted a discrete leptomeningitis penetrating the parenchyma along the spaces of Virchow-Robin. In the central region of the right hemisphere a significant area of necrosis was observed near the trauma resulting from the inoculation and responsible for the hemiplegia observed clinically.

The inflammatory lesions were distributed as shown in Figure 4, producing very characteristic sections from front to back. The nodular, perivascular and glial infiltration occurred selectively on the cerebral cortex in the frontal and parietal areas; the temporal lobe was less affected; the occipital pole was almost undamaged; the thalamus and the sub-thalamic nuclei were massively infiltrated on both sides. The brain stem at the level of the mesencephalic tegmentum, the reticular substance, and the peri-acqueductal nuclei were particularly altered. The inflammation extended to the cerebellum

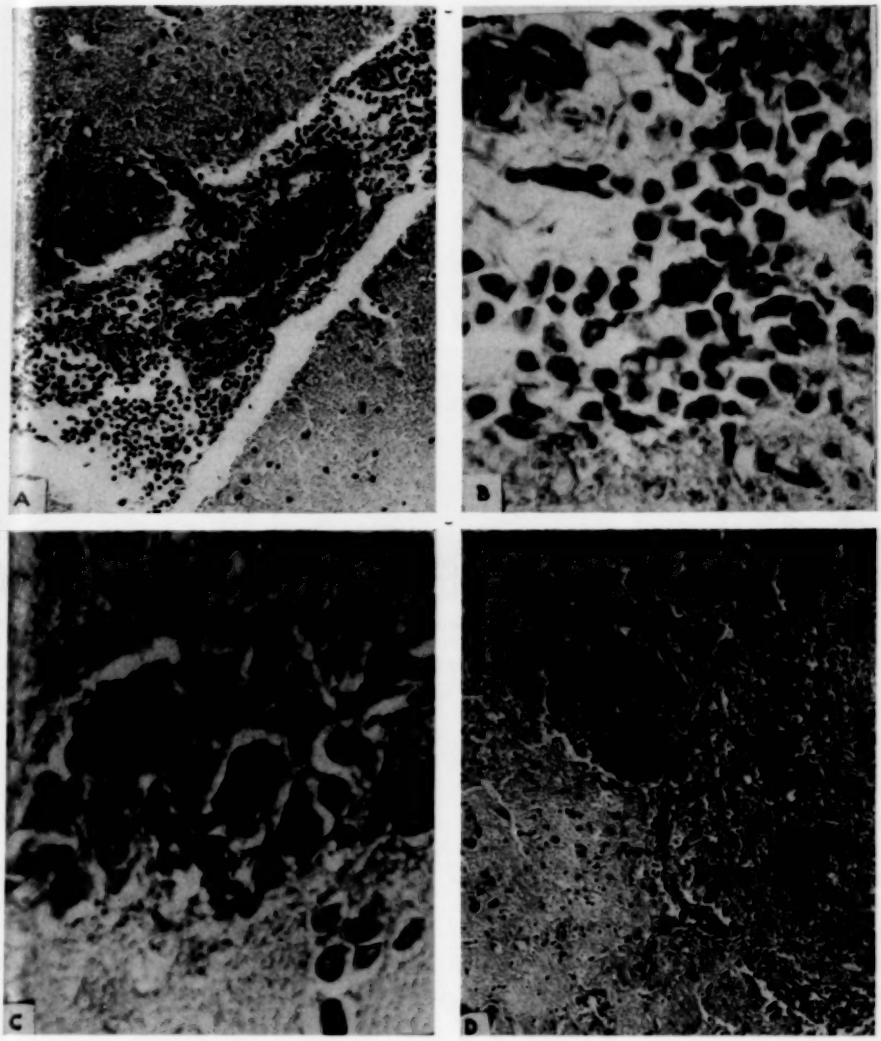

FIG. 2. Different aspects of the inflammatory infiltration (Monkey #2). A: Cellular infiltration of the pia-arachnoid, consisting essentially of lymphocytes with rare plasmocytes and some histiocytes. B: Perivascular infiltration consisting of the same elements, more easily recognizable at higher magnification. Note the histiocyte with abundant and finely punctate cytoplasm. C: Glial nodule constituted by a dozen microglial elements and astrocytes. D: Homogeneous necrotic focus, limited to the thalamus without any degree of cellular reaction at the point of contact. Note in the lower right corner the vessel with adventitial lymphocytic infiltration.

where it was seen most clearly in the molecular layer.

Monkey #3. An animal aged three to four years was inoculated on September 6, 1955, and received 0.5 cc of a 1/10 suspension 15 days old. The first clinical signs of disease appeared on September 13; the animal was prostrate and refused food; there was no

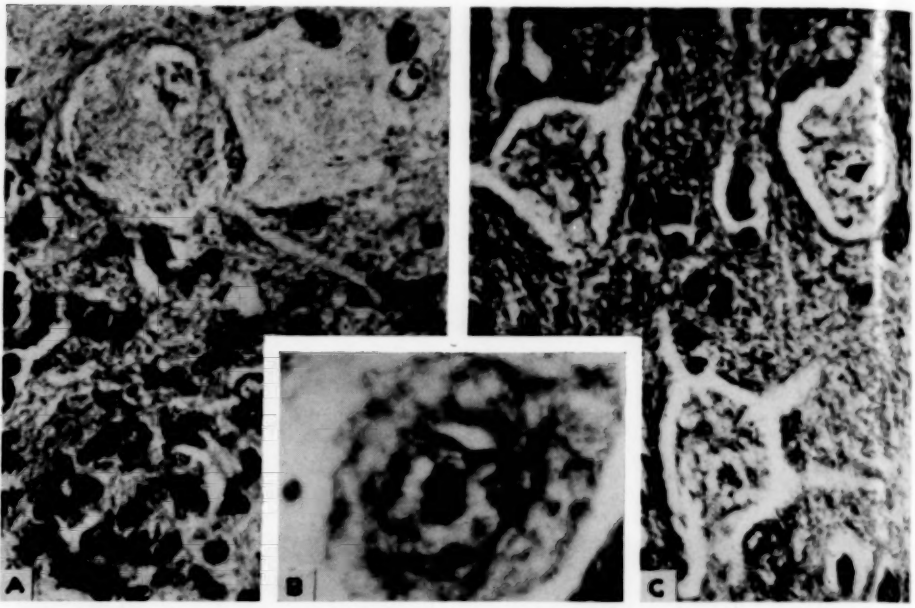

FIG. 3. Different aspects of cellular degeneration; Monkey #3. A: Polymorphic glial nodule in contact with two altered neurones which are hypertrophic and caryolytic; penetration of the cytoplasm by two glial cells. B: Vacuolation of cytoplasm; large nucleus surrounded by a clear halo; condensation of chromatin at the periphery of the nucleus. C: Micro-vacuolar degeneration of the cytoplasm affecting three neurones.

focal symptomatology. The animal was sacrificed on September 14, the eighth day following inoculation.

Electro-encephalographic findings: September, 9. Tracings characterized by an alpha rhythm at 9–10 c.p.s. symmetric bi-synchronous and reacting well to opening of the eyes. These tracings could be considered normal.

September 11, 5:30 p.m. (Figure 6A). Alpha rhythm persists unchanged over the left hemisphere but with the addition of slow theta and even delta waves on the right hemisphere, especially in the middle regions where some slow spike activity coincided with the site of inoculation.

September 13 (Figure 6B). The alpha rhythm had almost entirely disappeared over both hemispheres and was replaced by a bisynchronous theta and delta dysrhythmia, predominantly frontal. The anomalies previously focalized over the right hemisphere were obliterated by the generalized dysrhythmia and could scarcely be recognized.

September 14, 9 a.m. (Figure 6C). The slow hypersynchronous dysrhythmia persisted but was no longer continuous; episodes of depression of electrogenesis occurred, with intervening slow waves in bursts of long duration.

September 14, 4 p.m. (Figure 6D). At the beginning of the recording there remained (Figure 6D, 1,2,3) only a few bursts of slow-wave activity between episodes of electrical depression. At the end of the tracing (Section 4) the generalized delta and theta dysrhythmia, with frontal predominance, entirely disappeared; it was replaced by slower rhythms having, however, great amplitude (1 c.p.s.) distributed bi-synchronously with posterior predominance.

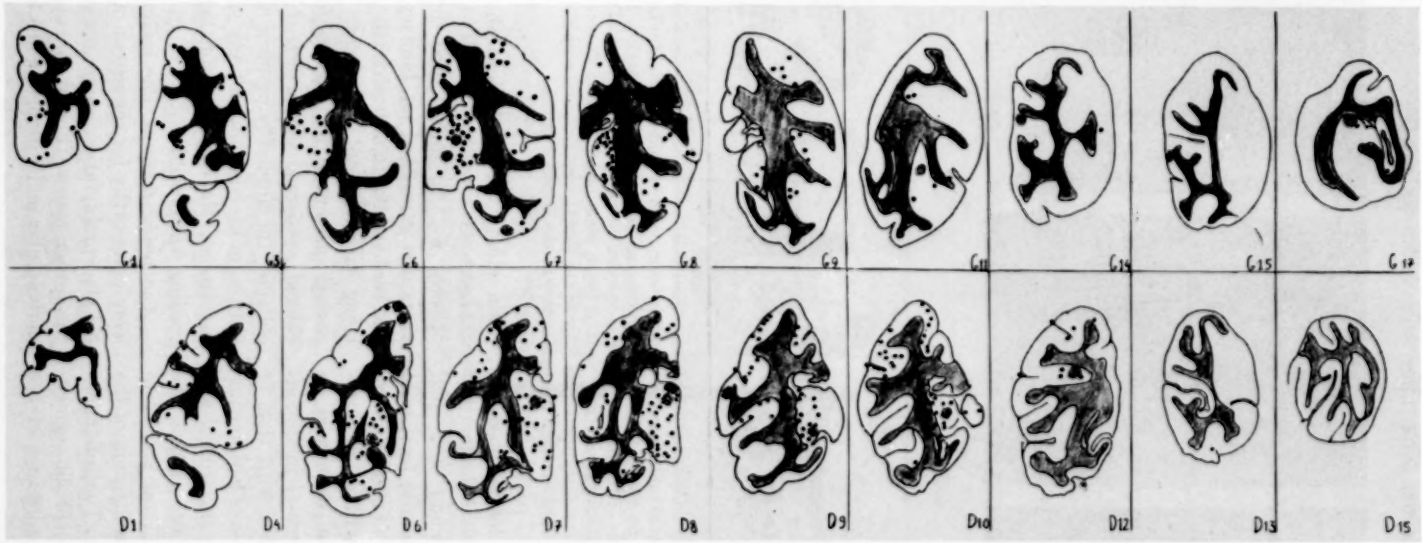

FIG. 4. Distribution of lesions in different areas of the left hemisphere (above) and right hemisphere (below): Monkey #2 (All the others presented a nearly identical picture).

The relative importance of perivascular nodules is shown by large dots, and in the case of glial nodules by collections of small dots. These nodules are selectively distributed throughout the gray matter. They are rare in the temporal cortex and in the occipital lobe where they are practically non-existent (despite the fact that the EEG dysrhythmia was generalized, and in this monkey was localized to the posterior head regions from the beginning of the infection). They are more frequent, however, in the subcortical gray structures, especially in the thalamus.

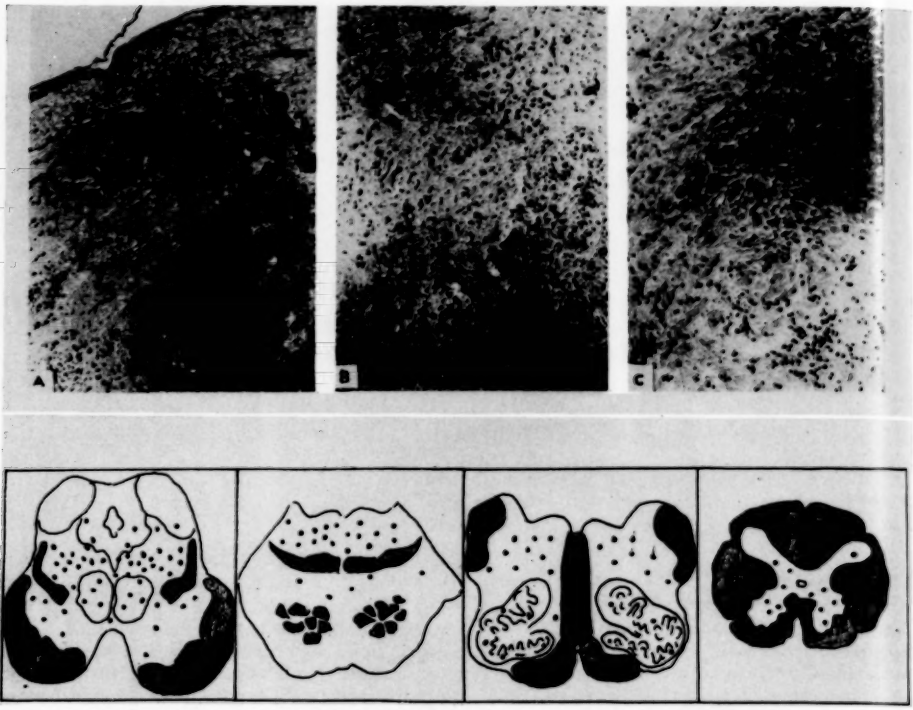

FIG. 5. Diffuse and nodular glial infiltration of the brain stem, such as that seen in Monkey #4 inoculated with a very virulent strain. Above: Three photomicrographs at different locations. Below: schematic representations of sections of the brain stem. *Mesencephalon:* massive infiltration of the tegmentum; red nucleus and substantia nigra involved; ventral brain stem intact. *Pons:* distinct lesions at level of the dorsal regions. *Bulb:* infiltration in the floor of the fourth ventricle and to a lesser extent at the level of the olives. *Cervical Cord:* damage predominantly in the anterior horns.

Anatomical findings. The lesions observed were noteworthy for 1) the inflammatory reactions, and 2) perivascular and glial nodules. There were no necrotic foci; mild cellular and axonal lesions (Figure 3) were present without selective distribution; a pronounced leptomeningitis had developed on the surface. The distribution of inflammatory lesions almost coincided with that of the preceding case; the degree of leptomeningitis was more pronounced; the frontal and parietal cortices were greatly changed, the temporal lobe and the occipital pole were relatively untouched. The infiltration of the thalamus was very marked. The inflammation extended to the mesencephalic tegmentum and to the reticular substance of the brain stem; the cerebellum showed little change.

Monkey #4. An animal aged three to four years was inoculated on January 15, 1957, and received 0.5 cc of fresh 1/10 suspension; being sacrificed on the seventh day. This animal presented an exceptionally acute clinical syndrome characterized by actual collapse, the animal lying on a heap on the bottom of his cage without any spontaneous movement. No electroencephalographic recording was possible.

Anatomical findings. The lesions observed were noteworthy for the extent of the nodular glial proliferation, more marked than in the other cases (Figure 5, upper). The perivascular infiltrations seemed less numer-

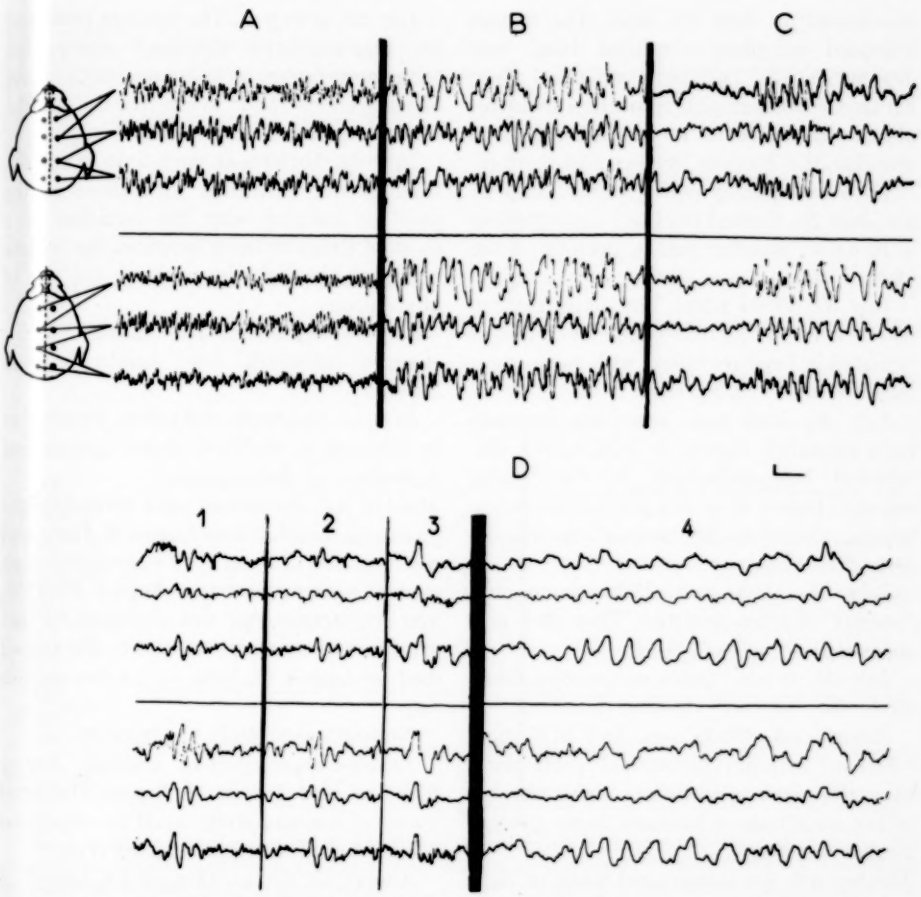

FIG. 6. Characteristic electrographic evolution of the encephalitis from an attenuated virus (Monkey #3). A: 11/9/55: Normal background alpha rhythm generalized over the whole scalp. Note the occasional slow waves and slow spikes over the anterior part of the right hemisphere (site of injection). B: 13/9/55: Loss of background rhythms; replaced by theta and delta, bilaterally synchronous and symmetrical, submerging the right frontal focal anomalies. C: 14/9/55: 9 a.m. Dysrhythmia now broken up into bursts by episodes of cortical depression. D: 1, 2, 3) The same day, 4 p.m. Depression more and more marked; bursts of hypersynchronous slow waves, growing shorter and shorter in duration (they were larger over the left hemisphere). D: 4) Same day, 5 p.m.: Hypersynchronous bursts have completely disappeared, as well as the background rhythms. The only remaining rhythms are very slow, continuous waves, predominating in the posterior regions where they show fusiform bursts. (Note that the cortical lesions are lacking in the occipital lobe of this animal; thus the waves here are transmitted).

ous; vascular congestion and edema were marked; no necrotic foci were observed; cellular and axonal degenerations were rare but did occur. There was less change in the cerebral cortex in this case where the major attack was bilateral and selectively on the thalamic and sub-thalamic structures; the nodular glial infiltration was equally extensive in the reticular substance of the brain stem (Figure 5, lower).

Monkey #5. An animal aged three to four years was inoculated on July 25, 1955; died on August 1, 1955; received 0.5 cc of fresh 1/10 suspension. First clinical signs were

manifested on July 29, 1955. The animal collapsed completely, refused food, was drowsy, rapidly becoming comatose. Only electroencephalographic recordings are available in this case as it was impossible to examine the nervous system post-mortem.

Electro-encephalographic findings. July 27 and July 29. Normal tracings; alpha rhythm 9/10 c.p.s.; reacting well to opening of the eyes.

July 30, 12:00 noon. The alpha rhythm had lost its continuous character and now occurred in fusiform bursts with some angular theta waves at 5–6 c.p.s.

July 30, 5:45 p.m. Two new elements have appeared: bursts of delta waves, distributed bisynchronously in the frontal regions; bursts of a 6 c.p.s. asymmetrical rhythm similar to the "arceau" rhythm described in humans.

July 31, 11:40 a.m. Delta waves and "arceau" rhythm persisted. They were now superimposed on each other.

July 31, 6 p.m. Delta waves diminished while the "arceau" rhythm remained.

August 1st, 10:30 a.m. and 6:25 p.m. "Arceau" rhythm diminished particularly over the right hemisphere; alpha rhythm of low amplitude in fusiform bursts present in all recordings.

Monkey #6. An animal aged seven or eight years was inoculated on July 18, 1955, and received 1 cc of fresh 1/10 suspension. First clinical signs appeared on July 21 1955, completely identical with those of the preceding case. The animal died during the night of July 25–26, *i.e.* on the seventh day. We have only electroencephalographic records on this case.

Electro-encephalographic findings. July 21, 11:00 a.m. and 6 p.m. Tracings characterized by background alpha rhythm at 9–11 c.p.s., bisynchronous and reacting well to eye opening, associated with theta waves at 6–7 c.p.s. predominant in the posterior areas. A focus of irregular delta waves was observed in the middle area of the right hemisphere, the site of inoculation.

July 22, 5:45 p.m. The tracings presented the characteristics described above, but there were bursts of 3–4 c.p.s. delta waves bisynchronous and symmetrical, in the frontal regions of both hemispheres.

July 23, 10:30 a.m. and 5:45 p.m. The tracings were identical with those of the previous evening with the addition of a focus of irregular delta waves in the middle region of the right hemisphere, the site of inoculation.

July 24, 11:30 a.m. The tracings had not changed although the amplitude was lowered.

July 25. Amplitude still lower, interrupted by intervals of electrical silence (generalized depression of electrogenesis).

Monkey #7. An animal aged seven to eight years was inoculated on August 6, 1955; and received 1 cc of fresh 1/10 suspension. First clinical signs appeared on August 12, 1955, and symptomatology was analogous to that exhibited by monkeys #5 and 6; the animal died on August 13, 1955, *i.e.* on the seventh day.

No anatomical study was possible.

Electro-encephalographic findings. August 9, 5 p.m. and August 11, 6 p.m. The rapid waves of low amplitude could be considered normal but of a desynchronized type.

August 12, 6 p.m. (Figure 7A, lower). A spectacular change in tracings; they were completely depressed and all former physiological activity disappeared; bursts of waves occurred from time to time being bisynchronous but very asymmetrical because of the much greater amplitude over the right hemisphere. These bursts commenced at 4–5 c.p.s. and slowed to 1–2 c.p.s.; they predominated in the frontal regions.

August 13, 6 p.m. (Figure 7B, lower). Immediately prior to the death of the animal the bursts described above disappeared and gave place to a complete electrical silence.

DISCUSSION

The material just presented can be divided into two distinct parts because of its rela-

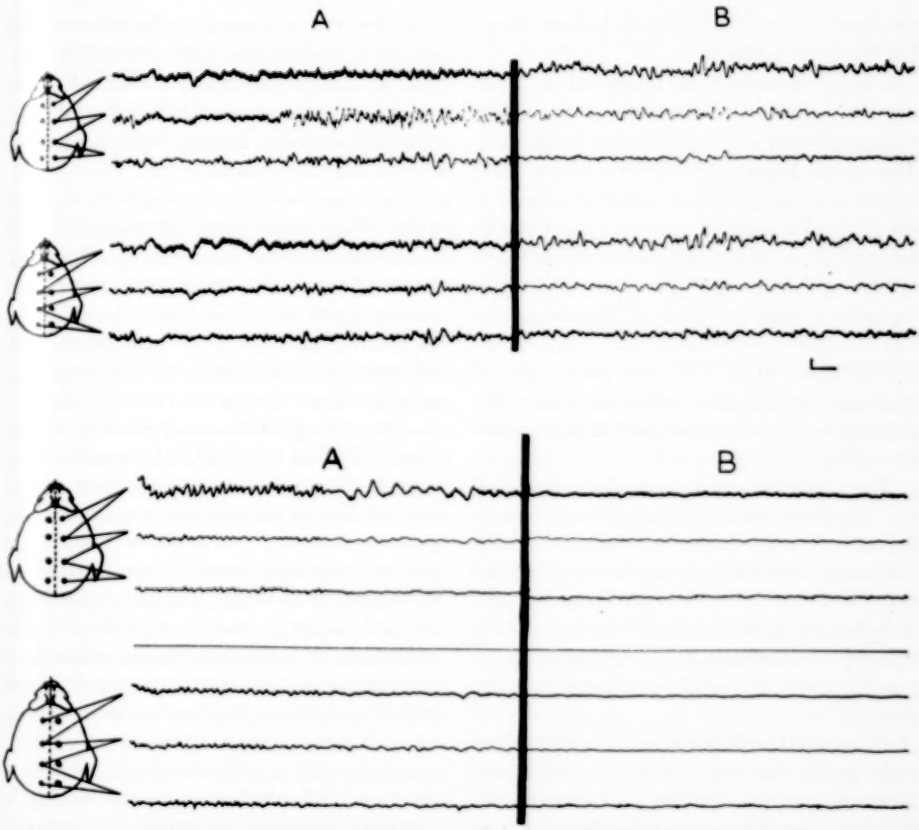

FIG. 7. Comparative electrographic evolution of the encephalitis following injection of an attenuated strain (upper tracing from Monkey #2) and of an encephalitis produced by a very virulent strain; (lower tracing from Monkey #7).

Monkey #2: Fragment of Record A: 20/8/55. Note that a theta and delta rhythm is already present, predominant posteriorly. Note also the rapid rhythms, mixed with short spikes in the right frontal area, *i.e.* at the site of inoculation.

Fragment B: 21/8/55. The irritative lesions of the right frontal area have disappeared. The slow dysrhythmias, which are bilaterally synchronous and symmetrical, are augmented and predominate in the anterior regions.

Monkey #7: Fragment A: 12/8/55. Slow rhythm, with little background alpha, indicating a depression of electrogenesis. Note the bursts of slow waves from the right frontal region, *i.e.* at the place of inoculation.

Fragment B: the following morning: Depressed electrogenesis is total, as indicated by a veritable electrical silence.

tion to the virulence of the inoculating strain. The first series of animals (Monkeys #1, 2 and 3) were inoculated with an attenuated virus; the second series (Monkeys #4, 5, 6 and 7) with an extremely virulent strain. We propose to discuss the clinical electroencephalographic and anatomical aspects of these two series of cases.

ANIMALS INOCULATED WITH ATTENUATED VIRUS

Three cases in this group demonstrated two distinct histo-pathological entities, accompanied by characteristic electrographic pictures. In one case we encountered an uncomplicated cerebral edema and in the other

two productive inflammatory lesions affecting the gray matter.

Simple exudative type. Observed in Monkey #1, this was characterized by edema associated with a diffuse vascular congestion. The edema appeared in three selective sites; 1) sub-meningeal with a vacuolar aspect in the molecular layer (Figure 1); 2) peri-vascular; and 3) in the white matter in the form of spongy areas and peri-oligodendroglial vacuoles. On the periphery of the edematous foci a rather discrete astrocytic reaction occurred. Associated with this were signs of neuronal involvement with an acute degenerative picture and occasional peri-vascular cuffing.

There were no apparent clinical signs, and no electroencephalographic changes were associated with these alterations which represent, therefore, the earliest anatomical manifestations of the disease. These changes included a notable exudative reaction while the signs of neuronal involvement, perivascular and glial reaction, were just beginning.

Although the EEG recordings were taken right up to the time when the animal was sacrificed, not the slightest electroencephalographic anomaly appeared. Thus, in the earliest stages of encephalitis, with no clinical signs but with a major cerebral edema, the electroencephalogram was of no diagnostic assistance. The neurones still appeared normal in structure and the serous extravasation predominated in the least dense areas of the cortex and in the white matter. It can be presumed that it did not interfere with the electrical activity in the parenchyma; this would explain the normality of the electroencephalogram and the absence of clinical signs.

The importance of this observation cannot be too strongly stated. It permits us to assume, contrary to the opinion given by most authors, that simple cerebral edema, (that is, serous extravasation not complicated by neuronal or vascular changes) causes no electrographic changes. In every case where slow waves, supposedly characteristic of edema, appeared, one must admit the existence of changes secondary to the edema or to its causes (productive inflammation, neuronal necrosis, hippocampal herniation, or vascular compression).

Acute encephalitis with an affinity for gray matter. Two of our cases (Monkeys #2 and 3) presented similar electroencephalographic abnormalities and analogous anatomical lesions. From the EEG point of view (Figure 6 and Figure 7, upper) these two animals followed a similar course. 1) The record remained normal during the first four days although cerebral edema was probably already present. 2) The first EEG abnormalities appeared at the same time as the first clinical signs of disease (drowsiness and hemiplegia) and demonstrated two types of change: the first being indications of diffuse cerebral involvement, the second, focal anomalies at the site of inoculation and contralateral to the hemiplegia. 3) In the later stages of illness, as a deepening coma supervened the focalized irritative elements became less severe while the diffuse anomalies became more pronounced, with a bisynchronous delta dysrhythmia. 4) In the last stages this dysrhythmia was increasingly interrupted by episodes of depression of electrogenesis.

These changes accord closely with the observations in Japanese "B" encephalitis in humans, made by Shimoda and Fukuda and also by Radermecker. These authors noted the same diffuse slow dysrhythmia (2-5 c.p.s.) of great amplitude, completely symmetrical in both hemispheres, and predominant in the frontal regions.

From the histo-pathological point of view both these animals showed the characteristics of an acute gray encephalitis; perivascular nodular and glial infiltration, predominant in the gray matter, selectively attacking the basal ganglia, the thalamus and sub-thalamic structures—where, in the case of Monkey #2, necrotic foci could be observed—(Figure 2 D.). The reticular substance, the dorsal nuclei of the brain stem and the dentate, all

showed the same productive reaction. A definite inflammation of the lepto-meninges was also found in one case (Monkey #3). A cerebral edema with vascular congestion and neuronal (Figure 3) and axonal changes of a spotty nature were identified in both animals. Neither of the two showed any demyelination. In both cases therefore, the inflammatory productive lesion represented the major element; it was formed of perivascular and glial nodules. 1) The perivascular cuffings developed from the perivascular adventitial element; they were mainly polymorphic in character with some mononuclear, plasmacytic and histiocytic macrophage elements (Figure 2A and B). 2) The glial nodules were of a different type; they were made up of larger monomorphic elements grouped without any obvious relation to the vessels (Figure 2C); these nodules were most often microglial in origin; in certain instances, moreover, they were associated with adventitial elements. The distribution of inflammatory peri-vascular and glial nodules is shown in Table 1. The topography of the lesions was almost identical in both cases (Figure 4), and showed that inflammation with affinity for gray matter selectively attacked the thalamus, sub-thalamic structures and the reticular substance of the brain stem.

These lesions correspond fairly closely to the changes in pathology in Japanese "B" encephalitis in the human. Zimmermann has stressed the existence of 1) meningeal involvement, 2) perivascular cuffing, polymorphic in nature, and 3) glial nodules mainly distributed in the gray matter, particularly in the basal ganglia, and in the brain-stem. However, the degenerative neuronal changes seem more marked in the human; this fact may be due to the longer duration of the development of obvious illness (five days as a minimum in Zimmermann's observations, 24 hours in our experimental studies.) In the case reported by Haymaker and Sabin, it was found that a lepto-meningitis persisted in the sulci in contact with the

TABLE 1

Percentage of Perivascular and Glial Nodules in the Brain (Monkeys #2 and #3)

	Thalamus and subthalamus	Cortico-nuclear gray matter (extrathalamic and subthalamic)	White matter
Monkey #2			
Right side	34%	54%	12%
Left side	40%	48%	12%
Monkey #3			
Right side	19%	61%	20%
Left side	31%	54%	15%

perivascular sheaths; the perivascular infiltrations and the glial nodules developed in the gray matter; they were distributed in the cortex predominantly in the region of the fissure of Sylvius, in the basal ganglia and the brain stem; the thalamus was acutely affected, the caudal nuclei, the putamen and the hypothalamus were less seriously attacked and the cerebellum was also affected.

The similarity of anatomical, electrographic and clinical evolution of these cases permits the drawing of certain conclusions with reference to the physiopathology of the encephalitides and of Japanese "B" encephalitis in particular.

1) The inoculation immediately responsible for a small local injury and for a rapidly developing generalized cerebral edema is not, however, followed by discernible electro-clinical manifestations. One must admit, therefore, that the liquid injected and the reactionary edema do not directly disturb neuronal function and that one cannot make the diagnosis of encephalitis before the appearance of productive lesions.

2) These productive lesions developing (a) at the site of inoculation and (b) at some distance, are expressed by clinical and electrical symptoms of different evolution.

(a) Focal lesions manifest themselves in an early and sudden manner by a contralateral hemiplegia and by localized electrical signs sufficiently irritative to produce epileptic phenomena accompanying the hemiplegia;

(b) The lesions at a distance usually proceed in a slower manner and, above all, more progressively. They eventually encircle all the focal lesions little by little.

From the clinical point of view there is a clouding of consciousness, then prostration, leading to coma which would persist if the animal were not sacrificed.

From the electrical point of view there was a bisynchronous dysrhythmia, predominant anteriorly, and of progressively slower frequency—first theta, then delta—with higher and higher voltages. This dysrhythmia was interrupted by episodes of generalized electrical depression affecting the entire electrogenesis.

There is no doubt, to-day, that such clinical features point principally to a sub-coritcal origin and to the irritation, and later a depression, of the mesodiencephalic structures of the superior brain stem charged with the regulation of consciousness and with cerebral electrogenesis.

The anatomical studies of our own animals strongly support this theory in the particular case of Japanese "B" encephalitis.

The cerebral lesions are discretely localized in the superior brain stem and notably in the thalamus. It is therefore probable that the development of lesions occurring at the mesodiencephalic stage provoke clouding of consciousness and finally prostration and the slow dysrhythmia which submerges and renders progressively inapparent the focal clinical signs (paresis) and the electrical signs (focal slow waves and spikes). It is equally probable that the evolution of these same lesions leads to a progressive depression of electrogenesis, which permits the persistence of only the bursts of slow waves. It is likely that these bursts will finally be replaced by electrical silence.

The focal signs from the injection are lacking in spontaneous Japanese encephalitis, but the diffuse signs persist and allow us to explain why this infection expresses itself principally as a coma with slow bisynchronous waves resulting from the preponderant if not selective injury of the brain stem and thalamus.

ANIMALS INJECTED WITH A VIRULENT STRAIN

Four cases belong to this group: Monkeys #4, 5, 6 and 7. The clinical symptoms were common to all: sudden collapse, with the animal showing no further spontaneous movement and refusing to eat, the clinical picture evolving quickly in the direction of coma and death.

From the EEG point of view animals #5, 6 and 7 were sufficiently similar to allow one to construct a pattern which contrasts with that following inoculation with attenuated virus (Figure 7, lower part). That is to say, there seems to be an initial period of four to five days with neither clinical nor electrical sign. Yet in the second stage the changes in consciousness and abnormalities in electrogenesis appear with an entirely different intensity; these clinical signs develop extremely rapidly towards coma and death, despite the fact that the electrical signs, on the contrary, are much less marked than in the sub-acute forms. The latter show only a moderately slow dysrhythmia, with persistence of rhythms which are more or less physiological but evolve rapidly towards a final global depression of electrogenesis. It is not a matter of the focal electrical signs being less marked but rather that they are masked by the importance of the general dysrhythmia.

From an anatomical point of view the only case studied (Monkey #4) showed a diffuse edema with intense vascular congestion and very important focal glial proliferation although the perivascular nodules are less numerous. This point clearly distinguishes the case of our other two anatomical observations on gray encephalitis (Monkeys #2 and 3). Another characteristic is equally peculiar to this animal; the integrity of the leptomeninges and the importance of inflammatory lesion at the level of the reticular substance of the brain stem (Figure 5).

The quantitative distribution of the lesions in this animal are presented in Table 2.

It is clear that anatomical, EEG and clinical relationships should be treated with great caution, since there is available but a single autopsied case. However, we believe that we can fairly say that the evolution of this single case goes far to explain the electro-clinical manifestations seen in Monkeys #5, 6 and 7, which are clearly differentiated from those receiving an attenuated virus. We have seen that the lesions always affect the diencephalon as in the less virulent forms but, also, that they clearly predominate at the level of the mesencephalon and the reticular formation, which plays a major rôle in the maintenance of consciousness. One might therefore suppose that the early massive change in the reticular formation produces a sudden coma without modifying greatly the electrogenesis, which is rapidly depressed. If the depression is very rapid one sees the direct passage from normal rhythms to terminal electrical silence; if this depression is more progressive,one sees first slow dysrhythmias characteristic of encephalitis of an attenuated virus. Then, one sees episodes of electrical depression progressively longer and ending quickly in electrical silence.

TABLE 2

Percentage of Perivascular and Glial Nodules in the Brain (Monkey #4)

Monkey #4	Thalamus and sub-thalamic formations	Gray matter outside of thalamus	White matter
Right side	37%	60%	3%
Left side	35%	56%	9%

CONCLUSIONS AND SUMMARY

Seven monkeys were inoculated with the virus of Japanese "B" encephalitis intracerebrally. One or more electroencephalographic tracings were made daily. The animals were sacrificed after varying times and the nervous system examined by serial sections.

The first animal, inoculated with an attenuated virus, was sacrificed four days later before any clinical or electrical abnormality was evident. A generalized cerebral edema was the chief anatomical lesion. Thus, a lesion of a purely exudative character, i.e. simple cerebral edema, showed no clinical nor electrical sign. The slow waves which habitually characterize cerebral edema, have, to our mind, a totally different significance. Paralleling the productive inflammation in our cases, these waves suggested in other circumstances a complication of intracranial hypertension (hippocampal engagement or vascular compression).

Another two animals, inoculated with an attenuated virus, were sacrificed on the eighth day. Their EEGs showed a bilateral delta wave dysrhythmia, continuous at first, but later tending to fragment, predominanting in the anterior and middle cortical regions, reinforced episodically by bursts of fusiform delta waves. The anatomical picture was that of a major productive reaction, with discrete signs of neuro-axonal involvement. Perivascular infiltrations and glial nodules were situated in the gray matter, though sparing, relatively, the cortex and predominating at the level of the sub-thalamus and thalamus. The transmitted character of the delta dysrhythmia points to this location as the site of the inflammatory lesions. The same electrical anomalies and the same distribution of lesions are found in human cases of "Japanese B" encephalitis.

These facts have a still more general significance in that one finds in other types of encephalitis, analogous bilateral delta dysrhythmia which assumes the characteristics of a diencephalitis.

Another four monkeys were inoculated with an extremely virulent strain. They presented a consistent clinical picture: sudden prostration of the animal, with a rapid development of coma. The anatomical lesions were characterized by a massive infiltration of the brain stem (mesencephalic tegmentum). It was from this area that the electrical

and clinical anomalies arose. The sudden coma and flattening of the EEG tracing, and the electrical silence observed in one case, was thought to represent a cerebral catastrophe secondary to a massive involvement of the regulatory formations in the brain stem. In another two cases, the EEG showed, at once, the beginning of a typical encephalitis of gray matter since, closely correlated in time with the extension of the inflammatory process to the reticular substance of the brain stem, the electrical activity was entirely changed; being then analogous to that seen experimentally when part of the reticular system is removed.

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BOOK REVIEWS

HOLT, ROBERT AND LUBORSKY, LESTER. *Personality Patterns of Psychiatrists*, Vols. 1 and 2. (Menninger Clinic Monograph Series) Basic Books, Inc., New York, 1958. xiv + 386 pp. (I) $7.50. xiv + 400 pp. (II) $4.00

This is a strange publication. Its major topic is an investigation of methods for selecting psychiatric residents, conducted at the Menninger Foundation during the decade starting in 1946. It also touches on many, many other topics, such as historical discussions of selection research, psychiatry, psychiatric education, and recommendations for selecting candidates for psychoanalytic training. The title is to a degree unfortunate—there is much on personality traits of psychiatrists, but little on personality patterns; the subtitle (A Study of Methods for Selecting Residents) is more accurate, provided the reader realizes that the study is confined to psychiatric residents. In themselves, these are of course not essential defects. However, they are cited because they indicate the temper of the book.

Also indicative is the odd publication format. Basic Books is apparently distributing Volume I by itself, although both Volumes may presumably be obtained from the Menninger Foundation. This is regrettable, for Volume II contains data and exposition which are essential to an intensive study of this research investigation. No reader should be required to take the authors' interpretations and recommendations without an opportunity of examining all the relevant data.

The reader who wants to know how these psychologists studied various methods for selecting psychiatric residents, and what their conclusions were, can find out by reading about 40 per cent of Volume I together with about two-thirds of Volume II. He will learn that ratings and measures derived from interviews, projective tests, and other instruments were compared with later measures, especially with ratings by those who supervised the residents. The general questions is: how well do measures made at the time of application agree with measures of later performance as psychiatric residents? He will read an Odyssey, a most interesting and quite personalized account of this essay into selection research. For people concerned with selecting such residents, these books will be of some, perhaps considerable value. It will be of less value to readers with other than these special interests. To be sure, it contains much data bearing on general problems of selection and of psychological measurement, but the reader must weigh the evidence critically and carefully himself; the authors do not systematically examine the broad scientific implications of their findings, but prefer to state their recommendations to psychiatric colleagues who may wish to utilize psychological techniques in dealing with selection problems.

The format is attractive. The first-person style is easy to read, almost beguiling. The exposition is rather discursive. These characteristics may be appropriate for the small group of specialized readers for whom the book will be most useful.

As a research report, and in the opinion of this reviewer, the organization and presentation are unsatisfactory. The whole document is somewhat unsystematic, and reader must work hard to grasp exactly what the investigators did. While the tables are reasonably clear, some do not make explicit the exact group of subjects involved. There is no list of tables to facilitate cross-comparisons the reader may wish to make. The data are presented in such a way that the reader must recall what was said much earlier if he is not to be misled. For example, analyses were made of the

intercorrelation or overlap among the several ratings for various characteristics that were made by each source of evaluations of the residents: supervisor's ratings, peer ratings, and ratings by each diagnostician using test materials. In each set of such ratings, one common factor, one general impression or evaluation was found: as frequently happens, the raters were largely unsuccessful in differentiating the several characteristics they rated. Yet the associations between personality ratings by diagnosticians and criterion ratings by supervisors are, in one place, analyzed trait by trait without reference to the previously presented internal analysis of these ratings. In view of the essential lack of differentiation among the traits, such discrete analyses have questionable value.

The authors are candid, disarmingly so, in pointing out their own oversight and their predictions which did not come true. However, at times they seem unaware of a certain psychometric naivete. Thus they appear to confuse psychometrics with statistics, the quantification of psychological data with the analysis of quantified data by methods which are not at all specific to psychological data. They appear less than familiar with major developments during the last several years with respect to the crucial concept of validity.

Whether or no this review is somewhat overcritical must be left for readers of the book to decide. Certainly there is much of value here, and the account represents an enormous amount of work. But the reviewer was unhappy to see recommendations offered gratuitously and *ex cathedra*. He would also have liked to see conclusions pointing out the congruence between the findings of this study and those of other similar investigations. For example, the findings are consistent with the established generalization that appropriate techniques can be empirically identified for predicting performance in a given special training program; that the success of such predictive measures will ordinarily be low but economically and socially worthwhile; and that the relative success of such a selection program is largely a function of the objectivity and specifiability of the measures for evaluating the performance to be predicted.

Donald W. Fiske

The professional mental healer enjoys a unique role in our society. As a recognized guardian of some of mankind's most mysterious "secrets," he is regarded with a mixture of respect and hostility not accorded the average physician. It has also been suggested that he does not bring the average physician's personality and predilections to his task. A possibly irrelevant light upon the psychiatrist as a person was cast by a poll conducted before the last national elections. It revealed that while approximately 85 per cent of physicians preferred Dwight Eisenhower, approximately 70 per cent of psychiatrists preferred Adlai Stevenson. Does this reflect the "democratic" point of view of the good psychotherapist?

Those of us who have been involved in the training of psychiatrists and psychoanalysts have become increasingly concerned with the products of our residency and institute programs. This concern is part of an increased sensitivity to our professional identifications. Perhaps the most familiar questions revolve about the issue of psychiatry as a medical specialty versus psychiatry as a basically psychotherapeutic discipline which utilizes little of its practitioners' previous medical training. Of the Winter VA Hospital residents between 1946 and 1950, who constituted the research group described in Holt and Luborsky's study, the most highly regarded were those characterized as good psychotherapists. It is probably true that in most major training centers, a resident's prestige depends more upon his reputation as a skilled and "sensitive" psychotherapist than upon any

other single item; this, despite the fact that such reputations are not always earned by the most dependable men nor those with the academic and research interests which are rewarded by junior staff appointments. Training faculties seem to be in conflict between their need to emphasize the many functions and the multi-disciplinary training of the psychiatrist and their tendency to place particular emphasis on the resident's psychodynamic understanding and psychotherapeutic acumen. Such conflicts inevitably influence the selection of candidates for residency training.

From the scientific point of view, this book (Volume I) is primarily the record of an attempt to devise techniques for the selection of psychiatric residents who will become "successful" in their chosen work. But its major appeal does not lie in its value for science. It is contained in the narrative accounts of the progress of individual residents, in the anecdotal flavor of the conclusions about what might be called "resident characterology," and in the authors' candid discussions of the suggestions and admonitions of leaders in the field who have attempted to distill their own experiences with selection.

It is hardly surprising that, after their massive research effort, the authors can offer no hard and fast predictive criteria for resident success. Interviews by experienced clinicians seemed to be more useful than most testing devices. Further, those elements suggesting potential success as a psychiatrist appeared to be non-specific. The interviewers responded less to a uniquely psychiatric personality pattern than to the "good man" who could deal intelligently, adequately, and perceptively with himself and others, no matter what his particular profession. There was a great deal of initial concern with the possible differences between those personalities who might become good psychoanalytic therapists and those who might do well as supportive therapists or administrative leaders. Here, too, when all of the evidence was considered, it was not possible to draw clear-cut conclusions.

This is a good book for psychiatrists who work with residents. It offers no specific answers, but it takes up many of the questions which arise in an active training center and deals with them in a candid, straightforward and informative way.

Eugene B. Brody

JUNG, C. G. *Aion: Researches into the Phenomenology of the Self.* (Collected Works, Vol. 9, Part II) Pantheon Press, New York, 1959. xi + 344 pp. $4.50

Freud once observed of his disciple turned dissident that he liked Jung better when he was still satisfied to be a doctor, and did not aspire to be a prophet. Those who share Freud's judgment probably will consider *Aion* as continuing a trend away from psychiatry, as commonly defined, into esoteric and possibly profitless research. The trend already evident in previously published volumes of the *Collected Works* (especially *Symbols of Transformation,* Vol. 5; *Psychology and Religion: West and East,* Vol. 11; and *Psychology and Alchemy,* Vol. 12), is carried further in this collection of "researches into the phenomenology of the self."

Yet, for Jung, this publication, and the more popular presentations of his findings and concerns contained in his recent essays on *The Undiscovered Self* and *Flying Saucers: A Modern Myth* . . . , form an integral part of his scientific and therapeutic endeavor. He insists repeatedly that he writes as an empiricist and "with the physician's sense of responsibility," as a phenomenologist and not as a philosopher or preacher. He does not pretend to be an historical scholar, and recognizes that he is opening himself to criticism from "the experts," as well as from his confused psychiatric colleagues, in entering into fields of study foreign to his medical training.

Why then does Jung consider it neces-

sary, *as a physician* specializing in the treatment of mental illness, to move beyond the customary analysis of dreams and free associations to alchemical drawings of the Middle Ages and the doctrines of both Western and Eastern religions? He is impelled by his experience, in analytic practice, of what appears to be a "universal language" of the unconscious, a language employing themes and symbols often apparently unrelated to the specific life experiences of the individual, but directly analogous to the symbols and myths produced by other peoples widely separated in space and time.

Over the past fifty years, Jung has become increasingly convinced that these symbols represent "archetypes of the collective unconscious"—"innate dispositions to produce over and over again the same, or similar mythical conceptions." They are the conceptual structures in terms of which men and women, of all times and places, perceive the world and represent it. The archetypes themselves are for Jung still no more than working hypotheses, unobservable and in a final sense unprovable. But, as with the electron in physics, they may help to explain that which is observable but otherwise not fully explainable.

Furthermore, he has become convinced that the most important archetype, the one which man most desperately needs to experience, or—in more Jungian terms—be "grasped by," is the self, the archetype of transformation in the search for wholeness and self-hood. It is through living "symbols of transformation," as they express the individual's emergent, potential self, that the unconscious contents can be assimilated into consciousness in such a way that they do not overwhelm or destroy, but rather give the individual "foundations" for his life. He thus finds creative resources which permit him to "be himself," rather than yielding to collectivization and conformity.

It is the purpose, then, of *Aion*, "with the help of Christian, Gnostic, and alchemical symbols of the self, to throw light on the change of *psychic* situation with the 'Christian aeon'." Jung considers, in particular, the symbol of the Fishes, as related to the Christian figures of the Son of Man and the Antichrist. He considers such an investigation necessary since "the archetypal image of wholeness, which appears so frequently in the products of the unconscious, has its forerunners in history." He seeks, in full realization of the difficulties of the undertaking and of his own limitations, to trace the relations between the traditional Christ-figure and the natural symbols of wholeness.

Such a statement of purpose will certainly discourage many readers from proceeding further. More, even for one open to the psychological consideration of religious doctrines, and well-oriented in Jungian concepts and terminology, this book is rough going. For after about thirty-five pages devoted to a quite clear and helpful discussion of the ego and the archetypes of the shadow, anima, animus, and self; one is soon immersed in the history of doctrine and astrological analyses, including "the prophecies of Nostradamus" and their fulfillment.

Indeed, for Jung the archetype of the self is "written" not only in human personality, but "in the heavens by projection" (p. 92). Thus, "The course of our religious history as well as an essential part of our psychic development could have been predicted more or less accurately, both as regards time and content, from the precession of the equinoxes through the constellation of Pisces" (p. 95). The "signs of the times" for the *present* age are not hopeful ones, as Jung reads them. We have lost the vitalizing archetype of the self in rationalism, intellectualism, and doctrinairism. We have lost the original, living spirit which can alone mediate and unite the "opposites" of life.

The busy psychologist or psychiatrist, if not already discouraged by the author's

statement of purpose, is apt to stop at this point of the argument, and skip the subsequent two hundred pages of documentation. For the general reader, this may be a wise judgment, since the substance of Jung's contributions concerning the nature of the self are contained in the first seventy pages. Here, as in his other writings, Jung considers the self as that which acts upon the conscious, volitional ego "like an *objective occurrence* which free will can do very little to alter." It is "the total personality which, though present, cannot be fully known," "an omnipresent, unchanging, and everywhere identical quality or substrate of the *psyche per se*" (pp. 5–6). This is the self—"a hypothesis . . . we are driven to . . . by the peculiar nature of the empirical material".

There is some evidence that this is a hypothesis which is gaining increasing acceptance in psychology and psychiatry. As Gordon Allport pointed out almost twenty years ago, "One of the oddest events in the history of modern psychology is the manner in which the ego (or self) became sidetracked and lost to view." In the 1880s, James and his contemporaries spoke freely of the ego, the self, or even the soul, in the attempt to explain the coherence, the unity, and the purposiveness which they considered to prevail in mental life. But positivistic psychology denounced all such concepts as question-begging and "theological," and except for psychoanalysis' emphasis on ego-functions, they were condemned to oblivion.

Since the Second World War, as Allport predicted, the ego (or self) has come back into respectability in psychiatry, though not in the *deus ex machina* connotations of pre-Wundtian psychology. In the development of neo-Freudian ego-psychology, the ego has been assigned an importance beyond that of the handmaiden of the id. In Erikson's research and writing concerning the problem of identity, still further revisions have taken place in the orthodox Freudian formulations of motivational variables. And, on the Continent, the development of schools of Existential Analysis and Logotherapy has brought increased emphasis on man's search for responsibility and meaning, beyond homeostasis or even pleasure.

A similar development has taken place in psychology, as "wholeness" has been emphasized by personality theorists in both the organismic and field theory traditions. Rogers' research in personality change during psychotherapy has led to increased attention to the relations between "actual self" and "ideal self," and Stephenson's Q-technique has been used to assess changes in this relation. Allport has introduced a new term into personality theory, to replace ego or self: "propriate functions . . . those functions that make for the peculiar unity and distinctiveness of personality, and at the same time seem to the knowing function to be subjectively intimate and important."

We seem in fact to be entering into a new era in psychology and psychiatry, with an emphasis on human potentialities, values, and "the magnitude of human and modern man." Texts in abnormal psychology written in the 1940s and revised in the 1950s *e.g.*, those of White, Maslow and Mittelmann, indicate a trend toward approaching psychopathology on the basis of a prior definition of the healthy or mature. We are beginning to distinguish between the normal, in the sense of a statistical average, and the normative. We are coming to the conclusion, as Fromm and others have asserted, that "adjustment"—the *sine qua non* of a "good personality" in the 1930s—is not necessarily a good thing if society itself is sick.

As much as any man, Jung may be said to have brought in this era, though few of the psychologists and psychiatrists who today make the emphases which he "pioneered" fifty years ago acknowledge indebtedness to him. Jung's painstaking de-

scription of the process of individuation and its preconditions, represents a tremendous contribution. For he realized long before most others that Freud's brilliant analysis of neurosis and its cure is only really adequate for people under thirty-five or forty years of age, wrestling with the problems of coping with one's environment and seeking to satisfy sexual impulses in a manner both personally satisfying and socially acceptable. For those in the second half of life, however, the key problem is meaning, and the craving is for "the four-fold gifts of faith, hope, love, and insight." This craving, he came to realize, is satisfied only as one is grasped by a larger wholeness —for the Christian, the God-image; for the psychologist, the self.

Aion carries forward Jung's investigation and reflections concerning these key issues. For the non-Jungian-specialist, however, little new of importance is added, and one is apt to find more stones than bread. From the author's standpoint, this volume is necessary, to document still further the historical parallels to the archetypes which he has found expressed in the symbolic productions of his patients. (It is difficult to evaluate the documentation, since for most readers and reviewers, the source materials used by Jung are not "at hand," and even more lacking are the technical skills of the "wise old man" in Zurich. One must realize, too, that this sort of documentation is only illustration of hypotheses, not evidence leading to proof, and that the interpretation of material presented proceeds from the author's assumptions and convictions.) But, for the non-specialist, this volume may produce more confusion than illumination. *Two Essays on Analytical Psychology* (Vol. 7) remains the best starting point for one beginning an exploration of Jung's writings.

Like many other volumes in the *Collected Works*, *Aion* will prove more valuable to the research or reference collection of a library than to the individual reader. This book is definitely not bed-time reading, unless one wants to dream in archetypes and constellations. Nor is it suited to between-patient browsing. Jung's contribution to the phenomenology of the self can be appreciated without following through on all of his researches. Indeed, if you do not believe in archetypes before you read the book, it will probably not convince you; if you do believe, you need not read it.

William Douglas

RUBINO, AGOSTINO. *Diagnostica Psichiatrica, vol. 2.* Casa Editrice v. Idelson, Naples, 1958. xiv + 443 pp., illus. 5500 l

The past thirty years in Italy have witnessed multiple approaches to the problems of mental illness and the appearance of so many different schools of thought that it has been very difficult, and at times almost impossible, for an Italian psychiatrist to remain independent or to follow an eclectic point of view. This disparity of opinions has had its advantages as well as disadvantages. While on one hand it has proven extremely stimulating for the research-oriented person, on the other hand it has failed to give the beginning practitioner a sense of security in his everyday work. A diagnosis made by a physician trained in any given school is often interpreted in a completely different manner from that of one trained in another setting. The textbook of Tanzi and Lugaro has been the only authority available to the medical student and the general practitioner, from which they could arrive at some order in their understanding of mental diseases. Each Professor, however, has usually arranged the publication of a short manual in which he expresses his own viewpoint, primarily for the use of his students.

The need for order in this somewhat chaotic situation has become so pressing that in the past five years a number of psychiatric textbooks has been published. One which certainly has presented the material

in a most comprehensive manner is the *Textbook of Psychiatry* of Bini and Bazzi (Rome), of which two volumes have already been published.

The book of Agostino Rubino, under review here, is the second part of a textbook of psychiatry, the first volume of which was published in 1954. The author is the Director of the Psychiatric Institute of the University of Palermo, and has been associated for many years with the school of Buscaino of Naples. Doctor Rubino's approach, as would be expected, has been heavily influenced by that biological viewpoint stressed by Buscaino for so many years. The following quotation clearly illuminates this. "Schizophrenia is a general disease with central nervous system manifestations. Buscaino noted a decrease in liver weight, digestive tract changes and sclerosis and activation of reticuloendothelium of the spleen and mesenteric lymph nodes. Liver chemistries were altered and deamination was blocked. He reasoned that the good effect of liver-bolstering therapy demonstrated that schizophrenic changes were due to a hepato-enteric toxin probably an amine acting on a predisposed central nervous system. He stated that the toxin probably produced lesions within the brain which resulted in psychic symptoms." Buscaino and Baruk, of course, belong to the neural humoral point of view which understands the alteration of the psychic functions as a consequence to exogenous and endogenous intoxication.

In the previous volume, dedicated to general psychopathological problems, Rubino essentially stressed the neurological basis of psychiatric symptoms, giving very little, if any, importance to the psychodynamic basis of these symptoms. Now, in this second volume, which is devoted to syndromes, he suggests the clinical application of the diagnostic methodology outlined in Volume I. The psychopathologic, biochemical, neurological, electroencephalographic and radiologic methods utilized in the examination of the patient are greatly stressed while very little attention is given to the psychologic and sociologic genesis of the psychiatric entities.

It is therefore understandable that the greater portion of this book is dedicated to a most complete description of the organic psychoses, mental deficiencies, amential and demential psychoses, epilepsies, etc., while the functional psychoses and character disorders are dealt with in no more than brief outline.

Nonetheless in the opinion of the reviewer this volume is of great importance, serving to reiterate that psychiatry is a branch of medicine and that medical methods may be fully utilized in the understanding of the majority of mental diseases. The book is richly illustrated with plates derived from the private practice of Doctor Rubino and will serve as a very useful general outline for workers in the field of psychiatry. Rubino announces a third and concluding volume which will be devoted to the classification of the clinical entities.

Edmund U. Wenzel

PATTERSON, C. H. *Counseling and Psychotherapy: Theory and Practice.* Harper & Bros., New York, 1959. xii + 322 pp. $6.00

The author focuses attention on two contrasting ways of dealing with people in the therapeutic relationship as well as in other fields of human relations. These may be characterized as attempts to understand on the one hand, and efforts to influence and control on the other. One's expectations upon reading the sub-title of this book can be used as a rough device to illustrate this distinction. If one reads the word "practice" to mean philosophy or attitude, then one might be in the "understanding" group. If one expects a discussion of technique as exemplified by Wolberg, for example, one might put himself in the "manipulative" group. Patterson indicates that to him psychotherapy is a matter of attitude and not

a series of behavioral manipulations which can be learned and then used to help others.

The theory and philosophy presented in a systematic fashion as a text for the advanced student is phenomenological psychology and client-centered psychotherapy. Beginning with an introduction which tries to define and differentiate counseling and psychotherapy and the necessary training to engage in these largely identical activities, the author discusses problems of ethics, values, and culture and their importance in the practice of psychotherapy. The bulk of the book is devoted to a discussion of the therapeutic relationship and contrasts two approaches to helping others: one characterized by a "positive, optimistic, encouraging view" based on "respect for the individual and his self autonomy" and the other, "a negative pessimistic discouraging view . . . which sees the individual as one who cannot take responsibility for himself who cannot be trusted to make his own decisions." The author, selecting the former approach, client-centered therapy, discusses the self from a phenomenological viewpoint, demonstrating how a psychotherapeutic attitude of understanding the patient as a unique individual while showing him genuine respect as a person of worth can help him to resolve his emotional conflicts. Problems of transference and counter-transference and the use of diagnosis and evaluation as viewed by various schools of therapy conclude this section. The book ends with a discussion of some current questions about depth psychology, psychotherapy as an art or science, and the elements common to all psychotherapy.

The book is clearly a partisan presentation, but nevertheless does serve a useful purpose in highlighting two apparently contradictory approaches to practicing psychotherapy. While there is very likely a difference in the philosophical thinking of therapists of the two schools, one is still left with a question as to whether or not there is not some essential similarity between the efforts of all successful psychotherapists. Patterson attempts to deal with this in his discussion of the common elements of psychotherapy but his resolution of the problem is not convincing. He suggests that authoritarian treatment leads to temporary results while the understanding treatment leads to a more permanent change, but admits a lack of evidence to support this position. It would seem to this reviewer that a more tenable and consistent position would be to maintain that understanding and respect for the patient are the *sine qua non* of therapy. Perhaps the manipulative therapist gets results with his patients only because in his own way he too conveys some understanding of, and some respect for the patient. This position would vitiate some of the clear-cut distinctions based on therapists' reports of what they do, between the two schools Patterson has contrasted; but it would be a logical extension of the theory he has presented.

The volume is documented with many diverse opinions on the subjects discussed and contains an extensive bibliography. These references are presented generally without critical evaluation and are largely expressions of opinion rather than presentation of experimental data. This is mainly a reflection of the state of our knowledge about therapy rather than a disinterest on the part of the author in research findings.

Although Patterson has written this book as a text for an advanced course in counseling or psychotherapy, it is not clear how an "advanced" course is defined. This reviewer feels that *Counseling and Psychotherapy* is a good text for a beginner in therapy at the graduate level prior to or accompanying practicum experience. The extensive survey of the literature should be particularly useful since it gives a broad picture of what has been written in the areas covered and the student can then seek out what particularly interests him.

Shabse H. Kurland

FREUD, SIGMUND. *Collected Papers*, Vols. 1–5. Basic Books, Inc., New York, 1959. 2,274 pp. $25.00

The London edition of the *Collected Papers* has been available—though certainly not easily obtained in this country—since 1925, when Volume IV was published. (Volume V did not appear until 1950.) An American printing of these 117 essays has, of course, long been needed, and the present publication is a welcome and highly important event. The five volumes include material spanning fifty years from 1888; in length the papers range from the 147 page case history of Little Hans (1909) to the two page sketch on "Medusa's Head" (1922). This collection of clinical notes and investigations, interpretative essays on behavior, art and literature, has surely stimulated more psychoanalytic thinking and has been more frequently cited in the literature than all the enormous remainder of Freud's writings.

Durably bound and well-printed, these books seem to be made for the hard usage to which undoubtedly they will be put. They are handsome volumes, more attractive than their respected predecessors. No further editing has been attempted, and apparently the printing plates of the standard British editions were used, for the text faithfully follows the original, page by page. In view of the frequency with which references have been and will be made to these articles, this is desirable and advantageous.

The content of each of the volumes is arranged chronologically, and accordingly illuminates the growth and change of Freud's ideas through the years. The development of the psychoanalytic movement as seen by its founder is to great extent recorded here as well. The fifth (posthumous) volume encompasses the greatest span of time; beginning with a short essay on "Hypnotism and Suggestion" written in 1888, it includes a small number of previously unpublished papers from the "early period," and some twenty articles written between 1925 and 1938.

The initial paper in Volume I is a memorial tribute to Charcot (1893); the articles which follow are of the early period, and conclude with "On the history of the psychoanalytic movement" (1914). Volume II is a collection of clinical papers and essays on various aspects of psychoanalytic technique written between 1906 and 1924. Among them appear "On the sexual theories of children," "Character and anal eroticism," "A child is being beaten," and "The dynamics of transference." Volume III includes the well-known five case histories so often used in psychiatric teaching; the Schreber case, the obsessional neurosis, the infantile neurosis, little Hans, and the briefer fragment of the analysis of the case of hysteria. Volume IV (and to some extent Volume V) includes metapsychological papers and essays devoted to the application of psychoanalytic principles to nonmedical subjects, as the famous "The Moses of Michelangelo" and "The taboo of virginity."

These five volumes, without which no psychiatric library whether institutional or personal will now be complete, are cased. On the box cover (and in the advertising circulars) appears an endorsing statement attributed to JNMD, as follows. "We recommend these collected papers to all interested in human behavior, for in them may be found the most important contributions to an understanding of this behavior that have as yet been offered to humanity." In point of fact this statement is the concluding sentence of a 1928 review, of the fourth volume only, of the Hogarth Press edition, and so is seen to have been appropriated, artfully enough, somewhat out of context. Without question, though, it is a statement which could, and should, apply to the entire collection: let it stand.

H. A. Robinson

WOLSTENHOLME, G. E. W. AND O'CONNOR, CECILIA M., EDS. *Biosynthesis of Terpenes and Sterols.* (Ciba Foundation Symposium) Little, Brown and Co., Boston, 1959. xii + 311 pp. $8.75

This is a collection of papers presented by research workers at a symposium sponsored by the Ciba Foundation. Even a casual perusal of the book reveals the great importance that the use of radioisotopes has assumed in the study of the synthesis of biological materials. Although a large number of the papers contain results obtained with isolated biological systems for example, mitochondria, there are some studies on whole animals and microorganisms. The text is printed in the same form as its predecessors in this series of Ciba Foundation Symposia, which have helped to keep research workers aware of the latest developments in their field of interest.

COOK, ROBERT P., ED. *Cholesterol: Chemistry, Biochemistry and Pathology.* Academic Press, Inc., New York, 1958. xii + 542 pp., illus. $15.00

The Editor states in the preface that this book should be of "use to scientific workers, not only those dealing directly with cholesterol but to all concerned with the wider aspects of biology, chemistry, and medicine." That he has succeeded can be ascertained by glancing through the table of contents. The various chapters, written by active research workers in the field, discuss topics such as chemistry, isolation, estimation, distribution, and localization in organisms and in tissues, and metabolism of cholesterol. The chapters, "Pathological Manifestations of Abnormal Cholesterol Metabolism" and "Treatment of Disorders of Cholesterol Metabolism," deal directly with medical problems. Although cholesterol is the main concern, many discussions include other steroids and lipides as well as the relationship between cholesterol and these substances. An appendix of laboratory methods is included for the practicing chemists. A careful reading of this appendix would be very instructive to anyone proposing to study any aspect of the main subject matter of the book. The presentation of the role of cholesterol in the nervous system is limited not because of its lack of importance, but rather reflects the amount of information that has been collected. The value of the book is increased by the inclusion of both name and subject indexes. This book will be the basic reference text for this subject for many years and should be on the book shelf of not only the research workers studying cholesterol and steroids but also those interested in any aspect of these substances.

Leopold May